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Review Article

Clonidine for the sedation of critically ill children: A systematic review

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Abstract
Objective. To summarize clinical research related to the effect of clonidine on sedation, signs and symptoms of withdrawal, and other adverse events among mechanically ventilated children.
Data Sources. We searched MEDLINE, EMBASE, CINAHL, LILACS and the Cochrane Central Register of Controlled Trials, trial registries and conference proceedings.
Study Selection. We included all observational and experimental studies that reported the transdermal, intravenous or enteral administration of clonidine to mechanically ventilated, critically ill pediatric patients.
Data Extraction. We extracted data on the effect of clonidine on sedation, withdrawal, duration of ventilation and adverse effects and did not attempt to quantitatively combine the results due to the heterogeneous study design and patient populations.
Data Synthesis. This review includes 4 case reports, two retrospective cohort studies (total of 58 children), two prospective uncontrolled studies (total of 55 children) and one randomized controlled trial (69 children). In general, efforts to minimize known sources of bias were modest and all studies used non-validated tools for measuring withdrawal. Small observational studies suggest an improvement in withdrawal symptoms and adequacy of sedation with clonidine therapy; however, the small randomized trial found no effect on these or on the duration of ventilation. Results of these small studies have limited generalizability and provide imprecise estimates of treatment effects.
Conclusions. Clonidine has been used as a sedative and analgesic agent to prevent and treat withdrawal in critically ill intubated children. Current clinical studies are inadequate to assess its benefits and harms, and do not support current widespread use.

Keywords: Sedation, clonidine, child, critical illness, mechanical ventilation, systematic review

Introduction

Most critically ill children who are mechanically ventilated require medications to reduce pain, anxiety and suffering, and to tolerate life sustaining interventions that are invasive, frightening and frequently painful. Effective sedation for children in the Pediatric Intensive Care Unit (PICU) requires careful balancing of the need for sedation with the adverse effects of sedative medications. Inadequate sedation may result in undue pain and suffering for children, ventilator dysynchrony, and risks accidental removal of life-sustaining supports such as endotracheal tubes and intravenous catheters. Excess sedation limits children's interaction with their parents and caregivers and may result in delayed weaning from mechanical ventilation and prolonged PICU stay with the attendant risks of increased morbidity. Other adverse effects from sedative and analgesic medications include hypotension, bradycardia, constipation and drug withdrawal when these medications are decreased or discontinued [1].

Clonidine is a centrally acting α_2 selective adrenergic agonist with multiple effects. Stimulating α_2 adrenergic

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receptors in the brainstem, it causes a decrease in sympathetic outflow and increased parasympathetic activity, reducing the release of norepinephrine and decreasing vasomotor tone and heart rate [2]. The mechanisms of analgesia are unclear, and may occur at the peripheral, spinal and central levels [3]. Sedation and anxiolysis may be caused by direct effects on the locus coeruleus, an area of the brain which may also be involved in opioid withdrawal [4].

Clonidine is widely but inconsistently used in critically ill children. Twenty-five percent of PICUs in Australia and New Zealand reported using clonidine in children with inadequate response to opioids and benzodiazepines [5]. Clonidine was not reported in one self-administered survey of Pediatric Critical Care physicians in the United States [6], while another one reported that 91.4% of units used drugs to prevent or treat withdrawal, most commonly methadone, lorazepam, diazepam and clonidine [7]. A survey of practice in the United Kingdom reported that "In the setting of more prolonged mechanical ventilation, a significant number of units suggested that they would use sedative agents such as clonidine, ketamine and lorazepam" and "the use of clonidine in this setting [withdrawal] was noted [8]." In a prospective observational study in the United Kingdom, 28 of 268 (10%) intubated patients received clonidine and 17% of patients experiencing withdrawal received clonidine [9]. A survey of German intensive care units reported clonidine was used in 36–56% of hospitals for the sedation of mechanically ventilated adults and 63% of hospitals used it during the weaning of sedatives [10]. Individual centres have reported: clonidine as a first-line sedative for approximately 85% of patients [11]; 9% of patients received clonidine after surgery for congenital heart disease [12]; and "clonidine is regularly used [13]".

Published guidelines for the sedation and analgesia of critically ill children recommend the use of clonidine in critically ill children [14,15]. The United Kingdom Pediatric Intensive Care Society Sedation, Analgesia and Neuromuscular Blockade Working Group Continuous recommends intravenous infusions of clonidine as an alternative to midazolam (grade of recommendation = D, based on case reports, case series, expert opinion or extrapolated from case control or cohort studies [15,16]). The Italian Society of Intensive Care Anesthesia and Analgesia recommends that "the sedative withdrawal syndrome is treated with α_2 agonists like clonidine and dexmedetomidine and/or with methadone [14]."

The purpose of this systematic review is to summarize the evidence for the effects of clonidine on sedation, signs and symptoms of withdrawal, and other adverse events among mechanically ventilated children in the PICU.

Materials and methods

Study selection

We included all observational and experimental studies that reported the transdermal, intravenous or enteral administration of clonidine to mechanically ventilated pediatric patients (using authors' definitions of pediatric). We excluded studies of clonidine pre-medication for anesthesia, and any studies that exclusively neonates.

We were interested in all clinically important outcomes including, but not limited to: level of sedation, occurrence and severity of withdrawal symptoms, any reported adverse effects, especially hypotension or bradycardia, duration of mechanical ventilation, and dose and duration of other sedatives or analgesics.

Searching

We searched for published studies using MEDLINE, EMBASE, CINAHL, LILACS and the Cochrane Central Register of Controlled Trials. We also examined trial registries, conference proceedings and the bibliographies of any identified studies and relevant reviews. We included all languages of publication. See Appendix A for the detailed search strategy.

Study selection

Two reviewers independently and in duplicate evaluated the titles and abstracts of all citations, then reviewed the full reports of all potentially relevant citations for inclusion in this review. Disagreements were resolved in discussion with a third reviewer if needed.

Quality assessment

In the absence of a single, universally accepted quality assessment tool for this heterogeneous group of studies, we used the following relevant factors adopted from the Ottawa-Newcastle Scale [17] to describe the methodologic quality of the included observational studies: (1) representativeness of exposed and control groups (Were the children selected in a manner likely to minimize bias such as consecutive cases? Were

reasons for non-enrollment reported if applicable?), (2) similarity between groups, (3) duration and completeness of follow-up, and (4) methods of assessment for level of sedation and withdrawal.

We used the following factors to describe the methodologic quality of the included experimental studies: allocation concealment, blinding, completeness of follow-up and methods of assessment for level of sedation and withdrawal.

Data extraction

We assessed the methodologic quality and extracted data using a customized, pre-tested tool.

Statistical methods and reporting

We did not attempt to quantitatively combine study results due to the heterogeneity of study designs and populations. Herein we present the results of observational studies and randomized controlled trials separately and summarize the results qualitatively.

Results

Study selection

We identified 551 unique citations, 13 of which met the inclusion criteria. Fig. 1 outlines the reasons for exclusion. Most excluded citations reported on the use of clonidine for indications unrelated to sedation or withdrawal. Chance corrected agreement for the duplicate selection of included studies was excellent (kappa = 0.87, 95% confidence interval = 0.7 to 1.0).

Description of included studies

Table 1 describes the studies included in this review. Children received 4.2–86 μg/kg/day of clonidine using intravenous, enteral and topical routes of administration. Four case reports each reported the use of clonidine in a single child for sedation, analgesia, prevention of withdrawal, or a combination of these [13,18–20]. Two retrospective cohort studies reported clonidine use for sedation and both the prevention and treatment of withdrawal in a total of 58 children [12,21]. Two

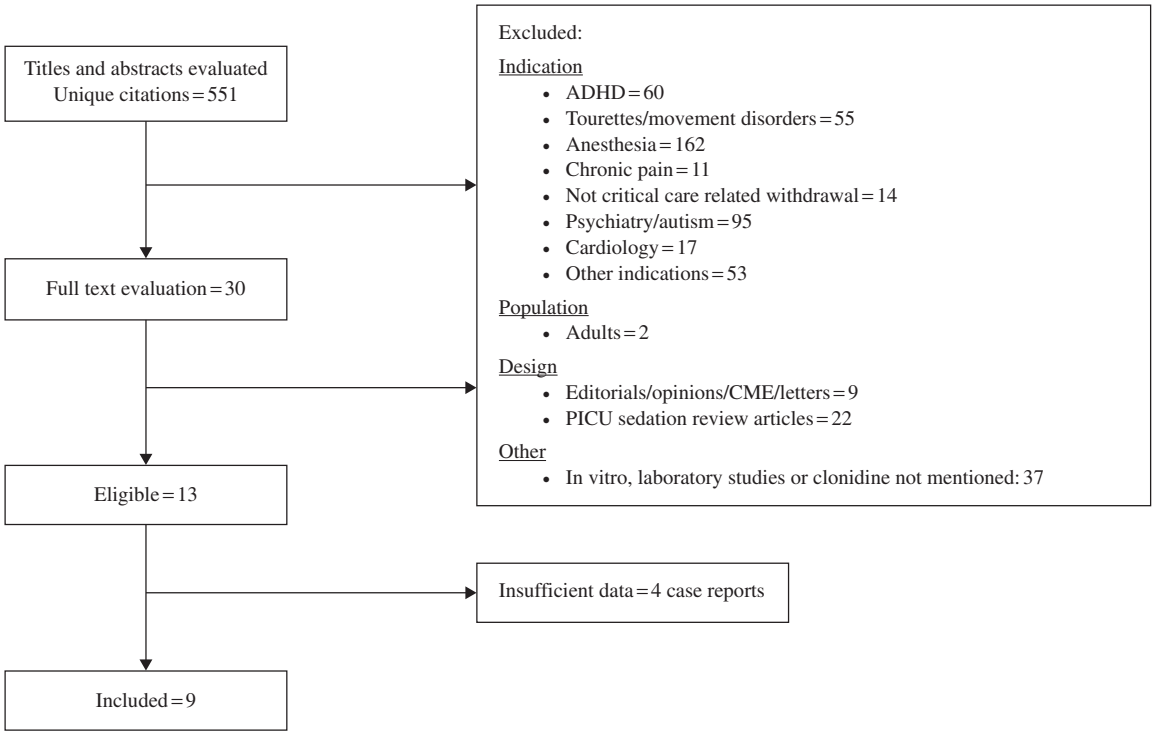

Fig. 1. Study selection.

Table 1
Description of included studies

Study	Direction of inquiry	Treatment Goal	Dose, route and duration of clonidine therapy	Inclusion criteria	Exclusion criteria
Case Reports					
Cho [18]	retrospective	treatment of withdrawal	2 μg/kg q6h enterally duration unclear	not reported	not reported
Cunliffe [13]	retrospective	sedation	1.4 μg/kg/h IV then 8.3 μg/kg enterally q6h for 12 days	not reported	not reported
Lowry [19]	retrospective	sedation and analgesia	1.7–4 μg/kg IV or enterally q8h and 0.3–0.5 μg/kg/h for 142 days	not reported	not reported
Lyons [20]	retrospective	analgesia	0.7–0.9 μg/kg IV q4h for at least 7 days	not reported	not reported
Cohort Studies					
Pohl-Schickinger [12]	retrospective	sedation and treatment of withdrawal	0.18–3.6 μg/kg/h IV for median 3 days (IQR 2–5 days)	0–24 months, post cardiac surgery, treated with IV clonidine for withdrawal symptoms	not reported
Deutch [21]	unclear	prevention of withdrawal	4.2–8.5 μg/kg/day transdermally beginning 12 hours pre-extubation for 7 days	post single stage laryngotracheal reconstruction who received more than 7 days of narcotic and benzodiazepines	simple anterior split, cartilage graft distal tracheoplasty
Uncontrolled Studies					
Arenas-Lopez [11]	prospective	sedation	3–5 μg/kg enterally q8h duration unclear	< 5 years of age requiring intubation for primary respiratory failure who was likely to need mechanical ventilation for longer than 72 h.	renal impairment liver impairment gastric intolerance inotropes arrhythmias complex congenital heart disease severe neurological impairment
Ambrose [22]	prospective	sedation	0.2–2 μg/kg/h IV duration unclear	ventilated, non-paralyzed children and post-operative cardiac surgical patients	not reported
Randomized Controlled Trial					
Molon [23]	prospective	prevention of withdrawal	5 μg/kg enterally q8h duration unclear	1–36 months, mechanically ventilated for >12 hours, infusions of morphine and midazolam	required discontinuation of morphine and midazolam and use of other sedatives, refractory hypotension, transfered or died during study period, exclusion requested by physician

prospective, uncontrolled studies reported the use of clonidine sedation in a total of 55 children [11,22]. One randomized controlled trial assessing the effect of clonidine added to morphine and midazolam on the incidence of withdrawal randomized 69 and reported data on 59 children [23].

Characteristics of patients in included studies

All of the included studies enrolled small numbers of patients. While all studies reported the administration of clonidine to mechanically ventilated children, there was clinically important variation in the age, diagnosis and other sedative medications used, as shown in Table 2. All patients received multiple sedatives and analgesics, most commonly opioids and benzodiazepines, at varying doses. Severity of illness measured by the Pediatric Risk of Mortality (PRISM) III score [24] or any other score was not reported in any study.

Methodologic quality of included studies

Table 3 presents a complete description of our quality assessment. Of the observational studies, only two reported the method used to select patients for inclusion: consecutive cases [21], and all patients who received IV clonidine for withdrawal symptoms [12]. The remaining reports did not adequately describe methods of patient selection, thereby precluding assessment of the potential for selection bias. The reasons for loss to follow-up or exclusions were inconsistently reported. Only one observational study reported any loss to follow-up (14 analyzed out of 25). These children were excluded from the analysis because they were extubated within 72 hours, were changed to IV clonidine for sedation failure or

Table 2
Patient characteristics

Study	Size	Age	Diagnosis	Sedation/analgesia used
Case Reports				
Cho [18)]	1	6 y	25% full and partial thickness burns	maximum: midazolam 0.8 mg/kg/h and fentanyl 20 μg/kg/h
Cunliffe [13]	1	1 month	bronchiolitis	chloral hydrate 200 g/kg/day, promethazine 4 mg/kg/day, midazolam 45 μg/kg/h
Lowry [19]	1	newborn	hemangioma and Kasabach-Merritt syndrome	fentanyl, lorazepam, midazolam, diazepam, methadone, chloral hydrate
Lyons [20]	1	11 y	78% 2nd and 3rd degree burns	morphine (maximum 15 mg/kg/day) and midazolam infusion
Cohort Studies				
Pohl-Schickinger [12]	50	5.0 months (3.0–9.0)[a]	post cardiac surgery	midazolam 7.58 μg/kg/min (1.26–11.22) or fentanyl 0.0 μg/kg/min (0.0–0.1)[a]
Deutch [21]	8	4.6 y (2.0–8.7 y)**	post single stage laryngotracheal reconstruction	morphine 100 μg/kg/h or fentanyl 2 μg/kg/h and benzodiazepine (20-100 μg/kg/h) initially
Uncontrolled Studies				
Arenas-Lopez [11]	24	3 months (1.3–15.9 months)[a]	acute viral bronchiolitis (13), pneumonia (4), and croup (3)	morphine 10–40 μg/kg/h and lorazepam 50–100 μg/kg as needed
Ambrose [22]	30	first 20: 12.5 months (7–38)[b] next 10: 2 months (0–15)[b]	not reported or post cardiac surgery	midazolam 50–100 μg/kg/h
Randomized Controlled Trial				
Molon [23]	69	clonidine: 21.5 (7.6–36) months[a], placebo: 13.5 (7.3–26.2) months[a]	indication for mechanical ventilation: 70% respiratory disease, 30% other	mean morphine 0.85 mg/kg/day and midazolam 8 mg/kg/day and intermittent benzodiazepines

[a]median (IQR)
[b]mean (range)

Table 3
Quality assessment of included studies

Study	Method of selection	Method of control selection	Similarity between groups	Duration of follow-up	Completeness of follow-up	Assessment of Sedation	Assessment of Withdrawal
Case Reports							
Cho [18]	n/a	n/a	n/a	post hospital discharge	1	not reported	assessed clinically
Cunliffe [13]	n/a	n/a	n/a	55 days post admission	1	not reported	scoring(13)
Lowry [19]	n/a	n/a	n/a	died on day 175 of admission	1	not reported	not reported
Lyons [20]	n/a	n/a	n/a	at least 40 days post admission	1	not reported	not reported
Cohort Studies							
Pohl-Schickinger [12]	all patients treated with IV clonidine for withdrawal	n/a	n/a	at least 6 days	enrolled: 50 analyzed: 50	not reported	symptoms, no scale reported
Deutch [21]	consecutive cases	Children who did not receive clonidine	yes	hospital discharge	enrolled: 8 analyzed: 8	not reported	modified NAS
Uncontrolled Studies							
Arenas-Lopez [11]	not reported	n/a	n/a	not reported	enrolled: 25 analyzed: 14 6 extubated before 72 h 3 sedation failure 1 protocol violation	COMFORT score targeting 13–23	not reported
Ambrose [22]	not reported	n/a	n/a	not reported	enrolled: 30 analyzed: 30	Modified OPS[a] targeting 2–7	not reported
Randomized Controlled Trial							
Study	Blinding		Allocation concealment		Completeness of follow-up	Assessment of sedation	Assessment of withdrawal
Molon [23]	reported as “double blind”		sealed numbered envelopes		enrolled: 69 analyzed: 59 5 deaths, 1 hypotension 1 physician request (one in each group)	targeted Ramsay Scale 4, actual scores not reported	NAS[b]

[a]Observational Pain Scale [36]
[b]Neonatal Abstinence Score [29]

because of protocol violations. Duration of follow-up was also inconsistently reported. Two observational studies reported using a standard sedation assessment tool (COMFORT [11] and OPS [22]). The randomized trial reported that unit practice was to target a Ramsay Score of 4 (indicating a brisk response to stimulus [25]) but the actual level of sedation achieved was not reported. The randomized trial of clonidine therapy was reported as 'double blind' and used sealed numbered envelopes for allocation concealment. Ten (14%) randomized patients were not included in the final analysis, including all patients who died. While patients who die before weaning of sedation cannot experience withdrawal, they are still at risk for the adverse effects of sedation which may complicate their care during their PICU stay.

One of the goals of many of these studies was to evaluate the effect of clonidine on the incidence, severity and/or duration of withdrawal. This goal is hampered by the lack of an accepted clinical definition or diagnostic criteria for withdrawal. Most tools used for assessing withdrawal in critically ill children, including the Neonatal Abstinence Score (NAS), were originally developed and tested in newborns exposed to opioids in utero [26–29]. Children in the PICU are often older and represent a broader range of ages and stages of development and the signs and symptoms of withdrawal may not be the same in all age groups. Children in the PICU are also exposed to multiple sedative medications and the symptoms of benzodiazepine withdrawal may be different than those of withdrawal from opioids.

None of these studies used an instrument validated in the PICU population [30,31] To measure withdrawal, one observational study [21] used a modified version of the NAS and another [12] reported the symptoms used to assess withdrawal, but did not report a formal assessment tool. The primary outcome of the randomized controlled trial used the NAS, originally tested in a group of newborns exposed to opioids in utero and it is unclear if the NAS is a sensitive or specific test for withdrawal in other populations. This may also explain the very high incidence of withdrawal, 75% in the placebo group and 72% in the clonidine group. While the true incidence of withdrawal is unknown, previous estimates among ventilated children range from 7.5 to 34% [9,32,33].

Effects of clonidine

Table 4 reports outcomes of the included studies. Two cases reported an improvement in withdrawal symptoms with clonidine and two others reported an improvement in analgesia. No adverse effects were reported. Two cohort studies (reporting on a total of 58 children) and two uncontrolled studies (reporting on a total of 54 children) showed an improvement in withdrawal symptoms and adequate sedation with a decrease in other sedative requirements with the addition of clonidine. Clonidine was well tolerated; one patient had clonidine held for hypotension and one case of self-limited sinus bradycardia was reported. Due to the lack of control group and the potential for bias, it is not possible to draw firm conclusions on the effectiveness of clonidine from these studies.

The single randomized trial found no differences in duration of ventilation (median 7 days and 6 days, p=0.4), sedation or analgesia requirements, or the incidence of withdrawal (72% and 75%, p=0.8) between patients who received clonidine or placebo, respectively [23].

Discussion

Clonidine has been used to facilitate sedation and to prevent and treat withdrawal in diverse populations of critically ill children. Uncontrolled observations suggest an improvement in withdrawal symptoms, level of sedation and decreased requirements for other sedative medications. In contrast, a single randomized trial of 69 patients using 5 μg/kg of enterally administered clonidine every 8 hours found no effect on the incidence of withdrawal, sedative doses or duration of ventilation [23].

Current research has helped, above all, to elucidate some of the challenges of inquiry in this field (primarily the need for validated assessment measures of sedation and sedative withdrawal). All of the studies included in this review, however, were limited by small sample sizes and provide imprecise estimates of treatment effects. Even for the randomized trial, generalizability is limited by the characteristics of the study population (children 1–36 months of age), the drug exposure (all children received morphine) and deep level of sedation targeted (Ramsay Scale =4).

This review summarizes the current state of clinical research evidence related to clonidine therapy in the pediatric intensive care unit. Future randomized trials in this field will advance current understanding if they (1) enroll a representative population of children with respect to age, diagnosis and severity of illness, (2) use clinically important outcome measures and validated assessment tools [30,34,35], (3) include children exposed

Table 4
Results of included studies

Study	Sedation	Withdrawal	Adverse effects	Duration of Ventilation
		Case Reports		
Cho [18]	not reported	Symptoms decreased: clonus, agitation, movement disorder, hypertension, tachypnia prior, only mild tremour after clonidine started	not reported	29 days
Cunliffe [13]	not reported	unclear	not reported	24 days
Lowry [19]	improvement in PIPP scores, decreased agitation	not reported	none	175 days (patient died)
Lyons [20]	allowed adequate analgesia at lower doses and decreased adverse effects of morphine and morphine decreased form 15 mg/kg/day to 1.4 mg/kg/day	not reported	not reported	34 days
		Cohort Studies		
Pohl-Schickinger [12]	significant reduction in midazolam and opioids after start of clonidine	clonidine decreased the symptoms of withdrawal by lowering MAP, heart rate, and core temperature	no episodes of hypotension requiring intervention, one case of self resolving sinus bradycardia (clonidine stopped), and no effect on cardiac rhythm	7 days (5–9)*
Deutch [21]	not reported	non-clonidine: 2/2 clonidine: 0/8 2 pts had symptoms on early removal of patch	1 patient had clonidine held for hypotension then restarted	groups not reported separately mean 7.7 days (range 7–8)
		Uncontrolled Studies		
Arenas-Lopez [11]	Adequate sedation for 837/1,022 (81.9%) h, oversedation and undersedation in 75/1,022 (7.3%) h, and 110/1,022 (10.8%) h respectively. Intention to treat: adequate sedation in 70.3% (1023/1456) h decrease in morphine (p=0.02) and lorazepam (p=0.03) requirements when clonidine started	not reported	no episodes of bradycardia requiring treatment, no recorded episodes of hypotension or hyperglycaemia	14 children: 3.4 days (3.3–4.6)[a]
Ambrose [22]	low dose/cardiac: 713/861 h in adequate sed range not including two failures high dose: 602/672 measurements in adequate sedation range	not reported	no bradycardia or hypotension or changes in cardiac index	not reported

Table 4. Results of included studies (Continued)

Study	Sedation	Withdrawal	Adverse effects	Duration of Ventilation
Randomized Controlled Trial				
Molon [23]	No differences in morphine or midazolam use or doses.	Incidence: clonidine: 72% placebo: 75% (p=0.8) Duration: clonidine: 3 days (0–10)[a] placebo: 4 days (0–10)[a] (p=0.6)	one patient withdrawn because of refractory hypotension (group assignment not reported)	clonidine: 7 days (7–10)[a] placebo: 6 days (5–10)[a] (p=0.4)

[a]median (IQR)

to a variety of medications and (4) include carefully considered and well described comparison groups such as usual care (typically opiates and benzodiazepines) or dexmedetomidine.

Clonidine has been used as a sedative and analgesic agent and to prevent and treat withdrawal in critically ill intubated children. While promising, its role for clonidine in sedation of critically ill patients is uncertain. Current published studies and frequent use mirror the growing clinical interest in the use of clonidine, but are as yet insufficient to evaluate the relative benefits and harms. Further observational studies and randomized trials will be helpful to fill this knowledge gap.

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Appendix A:

Search strategy

1. Databases: Ovid MEDLINE® In-Process & Other Non-Indexed Citations
   Ovid MEDLINE® <1950 to Present>
   EMBASE <1980 to 2008 Week 41>
   CINAHL

Date searched: 15/10/2008

Search terms:

1 exp Clonidine/
2 sedat*.mp.
3 child*.mp.
4 infant*.mp.
5 pediatr*.mp.
6 paediatr*.mp.
7 6 or 4 or 3 or 5
8 1 and 7 and 2

2. Database: LILACS

Date searched: 15/10/2008

Search terms:

1 clonid$
2 infant$
3 pediat$
4 sedat$
5 2 or 3 or 4
6 1 and 5

3. Database: Cochrane Central Register of Controlled Trials

Date searched: 15/10/2008

Search terms:

1 clonidine
2 sedat*
3 infant*
4 pediat*
5 child*
6 paediat*
7 3 or 4 or 5 or 6
8 1 and 2 and 7

4. Conference Abstracts

1 American Thoracic Society International Conference (2004–2008)
2 Society of Critical Care Medicine Annual Congress (2004–2008)
3 World Congress on Pediatric Critical Care (2003–2007)
4 European Society of Paediatric and Neonatal Intensive Care (2003–2008)

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