

Table S1 Characteristics of Randomised Controlled Trials, Controlled Clinical Trials and observational studies.

Study	Design	Population	Follow up/ duration of treatment	Dosing regime
				Loading dose (LD) and Continuous infusion rate (CIR)
Arya 2001[22]	RCT Midazolam (n=17) vs placebo (n=16)	Preterm neonates (mean gestation age: 31.5 weeks All infants were also receiving opiate infusion	48 hours of follow-up Duration of ventilation median=53 hrs Range=(7 to 216)	LD= 200 mcg/kg CIR=60 mcg/kg/hr
Anand 1999[23]	RCT Midazolam (n=22) vs morphine (n=24) vs placebo (n=21)	Preterm neonates (24-32 week gestational age; < 72 hours postnatal age Patients received opiates if required for analgesia/sedation	Study drug infusions were continued for as long as necessary or a max of 14 days Ventilator support mean 14.2 hrs SD=11.1 Patients monitored until 12 hours after discontinuation of drug	LD=200 mcg/kg CIR=20, 40 or 60 mcg/kg/hr depending on gestation age
Jacqz-Aigrain 1994[25]	RCT Midazolam vs placebo	24 Preterm Neonates (mean gestational age: 32.1; < 48 hours postnatal age) Patients were allowed to receive bolus doses of opiates if required, but not continuous infusion	Patients monitored for 5 days of treatment but not to or following extubation Mean duration of treatment mean=78.7 hrs SD=30.9 hrs across midazolam and placebo groups	LD=Not administered CIR=30 or 60 mcg/kg/hr depending on gestational age
Parkinson 1997[24]	RCT Midazolam vs Chloral hydrate and promethazine	22 (1 day to 17 years) Both groups also received morphine infusion	Patients monitored after treatment cessation until patient breathing spontaneously Durations of treatment and lengths of follow up not described	LD= Not administered CIR=50 mcg/kg/hr starting rate. 300mcg/kg/hr maximum rate
Tobias 2004[21]	RCT Midazolam (n=10) vs	Infants (2 to 70 months) Patients received opiates if required for	Patients followed for 48 hours of treatment of which only 24 hours was midazolam.	LD=Not administered CIR=100 mcg/kg/hr

	Dexmedetomidine 0.25 mcg/kg/hr (n=10) vs Dexmedetomidine 0.5mcg/kg/hr.	analgesia/sedation	After 24hrs on midazolam or dexmedetomidine if mechanical ventilation was still necessary, the patient was switched to the alternative and the study continued Midazolam infusion duration mean=22hrs SD=8hrs	
Treluyer 2005[20]	RCT All infants (n=23) were treated with midazolam and different doses compared	Preterm neonates (>33 weeks gestation age; <28 weeks post-natal age) Patients did not receive opiates	Infusion continued for up to 48 hours Median observation time period 12h (1-60)	LD=75 - 200 mcg/kg CIR= Each patient randomised to 37.5, 50, 62.5, 75, 87.5 or 100 mcg/kg/hr
Van Alfen van der Velden 2006[19]	RCT Midazolam (n=11) vs morphine (n=10) Patients treated with midazolam did not receive opiates	Preterm neonates (26-33 week gestational age)	Outcomes measured up to 120 mins after start of sedation only.	LD= 200 mcg/kg CIR= 200 mcg/kg/hr
Bergman 1991[38]	Retrospective Cohort (n=45)	mean=3.94 years range=(0.03 years to 19.2 years) Patients also received opiates	Duration of treatment: Mean infusion time 128 hours (range 12-917) Length of follow up not described.	Maximal dose received: 230mcg/kg/hr (70-940) Mean Total dose received: 29.8mg/kg (1.4-286)
Booker 1986[40]	Prospective cohort (n=50)	(6 months to 9 years) All children were also administered morphine	Duration of treatment: Mean=46.7hr Range=(13-197hrs) SD=54 Length of follow up post extubation was not	Mean dose: 228mcg/kg/hr Maximal dose received: 564mcg/kg/hr

			described	
Ducharme 2005[27]	Prospective cohort (n=27)	(> 1 month to 19years) Opioids were also administered to some patients	Duration of treatment: Range: <1 day, >21 days Length of follow up post weaning not provided	Not provided
Fonsmark 1999[31]	Retrospective cohort (n=38)	(6 months to 14 years)	Duration of treatment: Withdrawal group: 4 days (range 1-13) Non-withdrawal group: 3 days (range 1-11) Length of followup post treatment not described	<i>Withdrawal group</i> : total dose 30.9 mg/kg (0.01-99.2) <i>Non-withdrawal group</i> : total dose 4.6 mg/kg (0.3-33) All children received 'analgesics, mainly morphine'
Franck 2004[28]	Prospective cohort (n=13)	(6 weeks to 28 months) All children also received opiates	Duration of treatment prior to tapering median=9 days range=4-18 Duration of followup 2 days after treatment discontinuation	Cumulative dose median 26.4 mg/kg (range 0-154).
Hartwig 1991[39]	Prospective cohort (n=24)	(26 days to 5 years) All patients were also administered fentanyl	Duration of treatment: mean =11.6 days range= (38hr-40 days) Length of follow up post infusion was not described.	Doses ranged from 50-400mcg/kg/hr
Hughes 1994[34]	Prospective cohort (n=53)	(6 days – 11 years) Patients did not receive concomitant opiates	Duration of treatment: range 22 – 429 hrs Duration of follow up: max of 1 week post	Maximal dose received (range) 25-720mcg/kg/hr

			patient being fully conscious in presence of withdrawal symptoms	
Ista 2008[26]	Prospective cohort (n=79)	Median age 3.4 months; range 0 days to 15.5 years 73 patients also received opiate infusion	Duration of treatment: Median 10 days (range 3-108) Withdrawal symptoms observed median 6 days (1 to 67)	Median continuous dose 176 mcg/kg/hr (range 25-397); Median maximal dose 300 mcg/kg/hr (range 25-700)
Jacqz-Aigrain 1992[36]	Prospective cohort (n=15)	neonates (29-41 weeks gestational age) 7 of the patients also received opiates	Duration of treatment: mean= 60 hrs SD=23.3 Samples taken up to 24hr post infusion	CI= 60mcg/kg/hr
Jenkins 2007[6]	Prospective cohort (360 children on PICU of which 268 were mechanically ventilated. 186/268 received midazolam)	(Median age 1.4 years, IQR0.33-7) Other sedative/analgesic agents were also used.	Duration of treatment: not provided Followup until PICU discharge median 3 days IQR 1-6 days	<i>Withdrawal group:</i> Median dose 2mg/kg/day (IQR 1.1-3.3) <i>Non-withdrawal group:</i> median dose 1 mg/kg/day (IQR 0.5-1.9)
Lloyd-Thomas 1986[50]	Prospective cohort (n=10)	(6 months to 8.75 years) All children were also administered morphine	Duration of treatment: Mean=23.4 SEM= 0.69 Length of follow up post extubation was not described	Mean dose: 186mcg/kg/hr Maximal dose received: 300mcg/kg/hr
Pepperman 1997[32]	Retrospective Cohort (propofol v non-propofol)	(9 days to 16 years)	Duration of treatment: Range 13 minutes to 11 days	Mean dose: 400mcg/kg/hr (range 10-4900)

	(n=61)	“Most patients” received supplementary opiates”	Length of followup not described	
Rosen 1991[37]	Retrospective Cohort (n=55)	(0-19 years) Supplementary opiates were prescribed as required	Duration of treatment: Median: 74hrs Range=(4-1272)hrs Length of follow up post infusion was not described	Mean dose: 55.2mcg/kg/hr (-/+32.4) Maximal dose received: 240mcg/kg/hr
Shekerdeman 1997[33]	Prospective Cohort (n=10)	(Median age 3.3 years Range: 0.4–13.6) All patients were also sedated with opiate infusion.	Duration of treatment: not provided Length of follow up not described	Range: 100-200mcg/kg/h
Sheridan 1994 [35]	Retrospective Cohort (n=24)	(7 months to 17 years) All patients were also treated with opiates	Duration of treatment: Mean= 16.5 days range=(4-56) Length of followup post extubation not described	Mean maximal dose received: 110mcg/kg/hr range (40-350)
Sheridan 2001[30]	Prospective cohort (n=28)	(6 months to 16 years) All patients also received opiates	Duration of treatment: Median: 15 days range 8-112 Range: (1.1 – 48.9) Length of follow up post extubation not described.	Median dose: 160mcg/kg/hr Dose range: 30mcg/kg/hr – 290mcg/kg/hr
Sheridan 2003[29]	Prospective cohort	(1.2 -13 years) Opioids were also administered	Average duration: 12.7+/-10.9 days Range: 2 – 33 days	Average dose: 0.15+/- 0.16mg/kg/hr

	(n=11)	Length of follow up post extubation not described	Dose range: 0.06-0.65 mg/kg/hr
For characteristics of case reports and case series of midazolam see table 5			