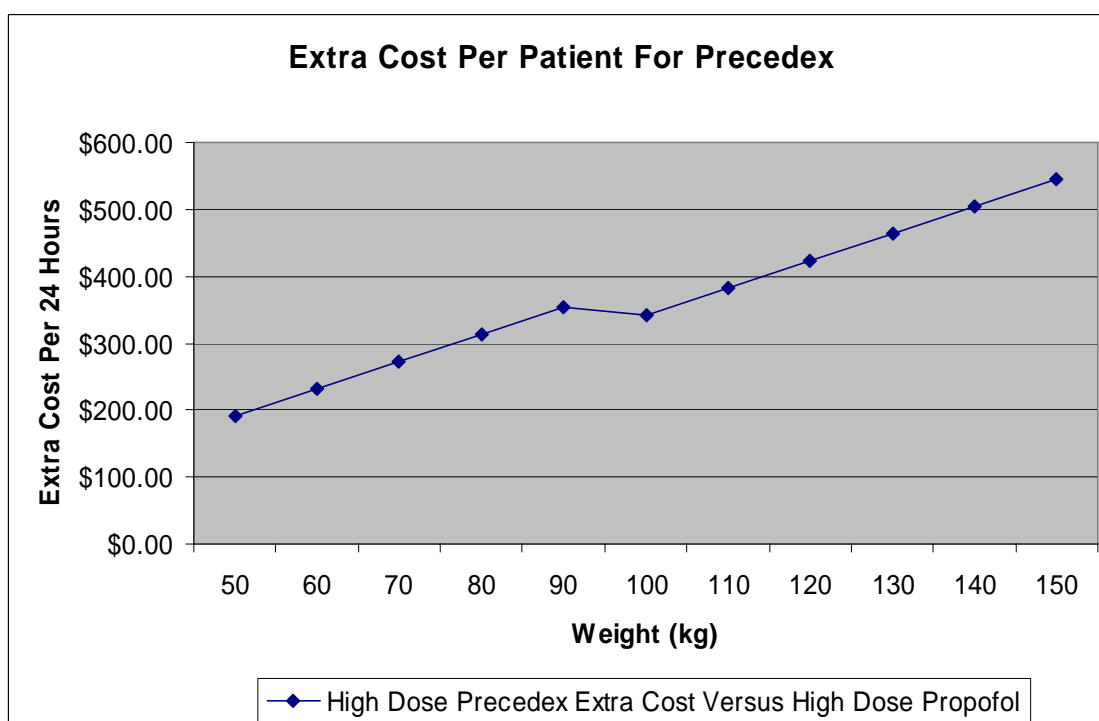


**Bon Secours Richmond  
Pharmacy & Therapeutics Committees  
Dexmedetomidine (Precedex)  
1/2007**

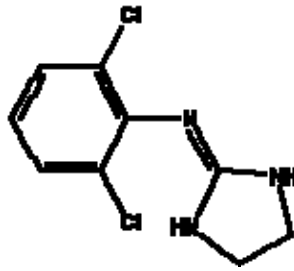
**Recommendations:**

- Dexmedetomidine (Precedex®) is recommended for provisional formulary addition, restricted to the following:
  - Cardiac surgery patients
  - Patients not tolerating propofol and benzodiazepines
- Dexmedetomidine's formulary status will be re-evaluated after 6 months. Outcomes for cardiac surgery patient's receiving dexmedetomidine and propofol will be compared for the following:
  - LOS
  - ICU/CCU Length of Stay
  - Time to Extubation
  - Mortality
  - Total Hospital Cost
  - Overall systemic infectious complications

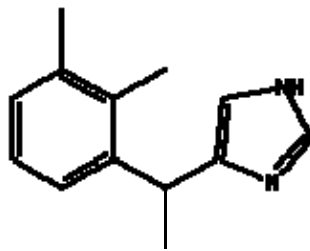


**Dexmedetomidine Overview**

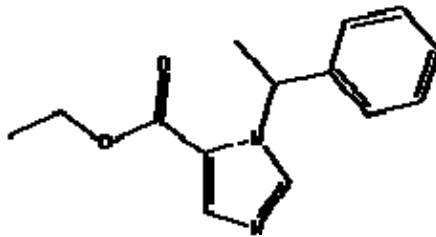
- Does not demonstrate clinically significant advantages over propofol.
  - Studies have failed to demonstrate significant differences in time to extubation, ICU length of stay, level of sedation, and mortality.
  - Opioid requirements are decrease but not eliminated by dexmedetomidine
- Alpha 2 adrenergic agonist, clonidine, dexmedetomidine) have been show to decrease perioperative cardiovascular complications with clonidine being studies most often.
- Is only indicated for up to 24 hours of use in intubated patients in ICU and may be used after extubation.
- It is not indicated in pediatric patients.
- It does not come premixed from the manufacturer.
- The loading dose must be administered slowly over 10 minutes by setting the IV pump at a rate 30 times faster than the maintenance infusion which may lead to dosage and administration errors.
- Side effect profile is similar to propofol without any advantages.
- The cost is 3.5 times higher than high dose Primary Propofol with secondary opioid in cardiac surgery. A conservative total cost increase for an equivalent number of patients from 2006 is \$37,171 for MRMC (1168 vials of propofol) and \$39,367 for SMH (1237 vials of propofol) for cardiac surgery.



Clonidine



Dexmedetomidine



Etomidate

## Findings:

- Dexmedetomidine is indicated for sedation of initially intubated and mechanically ventilated patients during treatment in ICU for up to 24 hours. It is not recommended during labor and delivery (including cesarean section).
- Dexmedetomidine is a selective central alpha<sub>2</sub> adrenoceptor agonist at low doses (10-300 mcg/kg) by slow IV infusion with sedation properties, and non-selective at high doses ( $\geq 1000$  mcg/kg) or with rapid IV administration.
- Dexmedetomidine may be given continuous infusion for up to 24 hours.
- Dexmedetomidine has not been shown to have amnesic properties, an important consideration for patients under neuromuscular blockade.
- Dexmedetomidine does not meet total analgesic requirements for ICU patients, but it does reduce the total amount of opioid required.
- Dexmedetomidine causes moderate blood pressure and heart rate reductions. During clinical trials in the UK 27% (18/66) of patients developed cardiovascular side effects, usually hypotension and bradycardia during the loading infusion (11/18) or maintenance infusion (7/18) which required interrupting or stopping the loading dose or maintenance infusion, pacing (4/18), IV fluid administration, or administration of atropine and inotropes (2/18). Nausea developed in 24% (16/66) of dexmedetomidine patients versus 9% (5/53) for placebo.
- Alpha<sub>2</sub> receptor stimulation decreases release of norepinephrine, inhibits sympathetic activity, decreases heart rate and blood pressure, produces sedation, anxiolysis, and analgesia.
- In clinical studies most patients received dexmedetomidine for less than 12 hours.
- Clinical significant episodes of bradycardia and sinus arrest have been associated in young, healthy volunteers with high vagal tone or with different routes of administration including rapid IV or bolus administration of dexmedetomidine.
- Overdose of dexmedetomidine or doses above 0.7 mcg/kg/hr can result in first degree AV block, second degree AV block, cardiac arrest, bradycardia, and hypotension.
- When used for pain control (0.4 mcg/kg) dexmedetomidine has a high incidence of sedation and bradycardia, which limits its use. Dexmedetomidine is less effective than oxycodone, requiring 3 doses of 0.4 mcg/kg for equivalent analgesia to 60 mcg/kg of oxycodone.
- During clinical trials of dexmedetomidine one patient received a loading dose of 19.4 mcg/kg in error and experienced cardiac arrest with successful resuscitation.
- The most common side effects of dexmedetomidine are: somnolence and dry mouth, increase BP during loading dose, hypotension, and bradycardia.
- Abrupt discontinuation of dexmedetomidine may result in withdrawal symptoms similar to those observed with clonidine, which include: nervousness, agitation, headache, rapid rise in BP, and elevation of plasma catecholamine concentrations. The package insert does not describe or give guidance on discontinuation.
- Long term use of dexmedetomidine may result in decreased ACTH stimulated cortisol release. A 40% drop in the cortisol response to ACTH was observed in dogs after a 1 week infusion of dexmedetomidine.
- Dexmedetomidine is the dextro-stereoisomer and active ingredient of medetomidine a veterinary anesthetic.
- A product license was refused in Europe.
- Drug interactions
  - Protein binding displacement of dexmedetomidine was minimal with fentanyl, ketorolac, theophylline, digoxin, digoxin, and lidocaine.
  - Protein binding displacement by dexmedetomidine of phenytoin, warfarin, ibuprofen, propranolol, theophylline and digoxin was not clinically significant
- Clinical Studies

Clinical Score	Level of Sedation Achieved
1	Patient anxious, agitated, or restless
2	Patient cooperative, oriented, and tranquil
3	Patient responds to commands
4	Asleep, but with brisk response to light glabellar tap or loud auditory stimulus
5	Asleep, sluggish response to light glabellar tap or loud auditory stimulus
6	Asleep, no response

## Studies from Package Insert

A randomized, double-blind, parallel-group, placebo controlled multicenter study was conducted with 353 patients in an intensive care setting. Patients were treated with dexmedetomidine (n=178) or placebo (n=175). The initial dose of dexmedetomidine was 1 mcg/kg given by intravenous infusion over 10 minutes. This dose was immediately followed by a 0.4 mcg/kg/hr infusion. The dose could be adjusted between 0.2 and 0.7 mcg/kg/hr to achieve a Ramsay sedation score of  $\geq 3$ . A rescue medication could be used if necessary. The rescue medication for this study was midazolam. Also, morphine sulfate was used for pain control, as needed. The target Ramsay sedation score was achieved without the use of rescue medication in 25% of the placebo group and 61% of the dexmedetomidine group (p<0.001). This score was achieved with 0 to 4 mg of midazolam in 19% of the placebo group and 20% of

the dexmedetomidine group. Fifty-six percent of the placebo group and 19% of the dexmedetomidine group required more than 4 mg of midazolam to achieve the target Ramsay sedation score. The mean total dose of midazolam was 19 mg in the placebo group and 5 mg in the dexmedetomidine group ( $p=0.0011$ ). Morphine sulfate was required for pain control in 81% of the placebo group and 56% of the dexmedetomidine group. The mean dose of morphine sulfate was 0.83 mg/hr and 0.47 mg/hr, respectively.

A randomized, double-blind, parallel-group, placebo controlled multicenter study was conducted with 401 patients in an intensive care setting. Patients were treated with dexmedetomidine ( $n=203$ ) or placebo ( $n=198$ ). The initial dose of dexmedetomidine was 1 mcg/kg given by intravenous infusion over 10 minutes. This dose was immediately followed by a 0.4 mcg/kg/hr infusion. The dose could be adjusted between 0.2 and 0.7 mcg/kg/hr to achieve a Ramsay sedation score of  $\geq 3$ . A rescue medication could be used, if necessary. The rescue medication for this study was propofol. Also, morphine sulfate was used for pain control, as needed. The target Ramsay sedation score was achieved without the use of rescue medication in 24% of the placebo group and 60% of the dexmedetomidine group ( $p<0.001$ ). This score was achieved with 0 to 50 mg of propofol in 15% of the placebo group and 21% of the dexmedetomidine group. Sixty-one percent of the placebo group and 19% of the dexmedetomidine group required more than 50 mg propofol to achieve the target Ramsay sedation score. The mean total dose of propofol was 513 mg in the placebo group and 72 mg in the dexmedetomidine group ( $p<0.0001$ ). Morphine sulfate was required for pain control in 85% of the placebo group and 59% of the dexmedetomidine group. The mean dose of morphine sulfate was 0.89 mg/hr and 0.43 mg/hr, respectively.

	<b>Propofol (Diprivan)</b>	<b>Dexmedetomidine (Precedex)</b>
<b>FDA Indication</b>	Induction & maintenance of anesthesia or short and long term sedation	Sedation of initially intubated and mechanically ventilated ICU patients for <b>≤ 24 hours</b> .  It is not recommended during labor and delivery (including cesarean section).
<b>Mechanism of Action</b>		Centrally acting Alpha2 adrenoceptor agonist similar to clonidine.
<b>Actions</b>	General anesthetic, sedative-hypnotic agent	decreases release of norepinephrine, inhibits sympathetic activity, decreases heart rate and blood pressure, produces sedation, anxiolysis, and analgesia
<b>Ages</b>	Adult and pediatric $\geq 3$ years old	Adults ( <b><math>\geq 18</math> years</b> )
<b>Onset</b>	40 seconds	Sedation: ND Analgesia 30 minutes
<b>Loading Dose</b>	Cardiac Anesthesia: 0.5-1.5 mg/kg over 1 minute (20 mg every 10 seconds)	1 mcg/kg over 10 minutes
<b>Maintenance Dose</b>	Cardiac Anesthesia Primary Propofol with 2 <sup>nd</sup> opioid: 100-150 mcg/kg/min Low Dose Propofol with Primary Opioid: 50-100 mcg/kg/min	0.2-0.7 mcg/kg/hour
<b>Maximum effect from dosage change</b>	3-5 minutes	ND
<b>Major Side effect</b>	When spontaneous respiration is maintained: <ul style="list-style-type: none"> <li>Hypotension (decreased preload &amp; afterload) 30% decrease, cardiac output <math>\pm</math> unchanged, HR <math>\pm</math> unchanged.</li> </ul> When ventilation is assisted: <ul style="list-style-type: none"> <li>Decrease in cardiac output is attenuated.</li> </ul> Apnea during induction with 2-2.5 mg/kg lasting up to 30-60 seconds, avoid rapid bolus injections Decreased ventilation & oxygen desaturation.  Dose dependent decrease in preload and afterload Bradycardia	Biphasic effect on the cardiovascular system. Loading dose is associated with vasoconstrictive effects resulting in bradycardia and hypertension. (Hypertension 20% increase MAP with decreased heart rate of 27% with loading dose) Continuous infusion is associated with hypotension. Hypotension > 20% reduction in 30% of patients, bradycardia
<b>Time to awakening</b>	Short term infusion (1-10 hours): rapid (3-8 minutes). Long term infusion (10 days): Longer time to awakening (20 minutes). Daily awakening and use of minimal effective dose maintains awakening in 10-15 minutes evening after long term infusion.	ND
<b>Pharmacokinetics</b>	Three compartment model	Linear with normal doses
<b>Clearance</b>	1.38-3 L/kg/hr  No change in chronic renal impairment No change in chronic hepatic cirrhosis	0.54 L/kg/hr No change for gender or 18 to > 65 years No change for renal impairment  % of Normal Clearance 74% Mild Hepatic Dysfunction 64% Moderate Hepatic Dysfunction

	<b>Propofol (Diprivan)</b>	<b>Dexmedetomidine (Precedex)</b>
		53% Severe Hepatic Dysfunction
<b>Fraction Excreted Unchanged In Urine</b>		None
<b>Metabolism</b>	Liver 50% Glucuronide Conjugate	Liver Glucuronidation and CYP-450
<b>Volume of Distribution</b>	60 L/kg after prolonged infusion 10 days	1.33 L/kg, 118 L
<b>T1/2</b>	14-30 hours Note: redistribution is main factor for elimination of sedation	2 hours
<b>Protein Binding</b>		94% Decreased in Hepatic Impairment No in vitro protein binding interactions with phenytoin, warfarin, propranolol, theophylline, digoxin.
<b>Cost Per Day, assuming 70 kg patient</b>	25 mcg/kg/min \$38.19 50 mcg/kg/min \$76.38 100 mcg/kg/min \$140.03	0.2 mcg/kg/hr \$106.88 0.4 mcg/kg/hr \$213.76 0.7 mcg/kg/hr \$320.64
<b>Pregnancy Rating</b>	Category B	Category C
<b>Preservative</b>	Benzyl Alcohol 1 mg/ml	

## **ADVERSE REACTIONS**

Adverse event information is derived from the placebo-controlled, continuous infusion trials of dexmedetomidine for sedation in the ICU setting in which 387 patients received Precedex®. Overall, the most frequently observed treatment-emergent adverse events included hypotension, hypertension, nausea, bradycardia, fever, vomiting, hypoxia, tachycardia and anemia (see Table 5).

Adverse Event	Randomized Dexmedetomidine (N=387)	Placebo (N=379)
Hypotension	28%	13%
Hypertension	16%	18%
Nausea	11%	9%
Bradycardia	7%	3%
Fever	5%	4%
Vomiting	4%	6%
Atrial Fibrillation	4%	3%
Hypoxia	4%	4%
Tachycardia	3%	5%
Hemorrhage	3%	4%
Anemia	3%	2%
Dry Mouth	3%	1%
Rigors	2%	3%
Agitation	2%	3%
Hyperpyrexia	2%	3%
Pain	2%	2%
Hyperglycemia	2%	2%
Acidosis	2%	2%
Pleural Effusion	2%	1%
Oliguria	2%	<1%
Thirst	2%	<1%

The treatment-emergent adverse events in Table 6 were reported in ≤1% of all dexmedetomidine-treated patients that are potentially clinically relevant.

[Am J Health Syst Pharm.](#) 2007 Jan 1;64(1):37-44.

## **Sedation and analgesia in the intensive care unit: Evaluating the role of dexmedetomidine.**

[Szumita PM](#), [Baroletti SA](#), [Anger KE](#), [Wechsler ME](#).

Department of Pharmacy, Brigham and Women's Hospital (BWH), Boston, MA.

**PURPOSE:** A review highlighting the application of sedatives and analgesics in the intensive care unit (ICU) setting, with a focus on the use of dexmedetomidine, is presented. **SUMMARY:** Relevant and applicable clinical trials that resulted from a search of the literature from 1966 to July 2006 using key search terms such as dexmedetomidine, intensive care unit, sedation, delirium, and analgesia were evaluated. Many agents have been evaluated in the search of the optimal regimen for sedation and analgesia in the ICU, including opioids, benzodiazepines, propofol, and antipsychotic agents. Dexmedetomidine has demonstrated efficacy as a sedative analgesic on the basis of its ability to lower opioid, benzodiazepine, and propofol requirements in clinical trials. The role of dexmedetomidine in ICU clinical practice is limited because of a lack of mortality and other morbidity endpoints, such as ICU length of stay, hospital length of stay, time to extubation, long-term complications after discharge from the ICU, and delirium. The most commonly reported adverse effects of dexmedetomidine are secondary to its effects as an alpha(2)-receptor agonist and are cardiac in nature. A detailed cost analysis may be warranted to justify the relatively high acquisition cost of dexmedetomidine. **CONCLUSION:** Dexmedetomidine may be an effective agent for ICU sedation and analgesia. However, the lack of clinically relevant endpoints in trials, the concern about adverse cardiovascular effects, and the relatively high acquisition cost of this drug limit its use to a select number of patients who may benefit from its distinguished mechanism of action.

[Am J Med.](#) 2003 Jun 15;114(9):742-52.

## **Alpha-2 adrenergic agonists to prevent perioperative cardiovascular complications: a meta-analysis.**

[Wijeysundera DN](#), [Naik JS](#), [Beattie WS](#).

Department of Anesthesia, University Health Network, Ontario, Toronto, Canada.

**PURPOSE:** To investigate the effects of alpha(2)-adrenergic agonists on perioperative mortality and cardiovascular complications in adults undergoing surgery. **METHODS:** MEDLINE (1966 to May 2002), EMBASE (1980 to May 2002), the Cochrane Clinical Trials Register, the Science Citation Index, and bibliographies of included articles were searched without language restriction. Randomized trials comparing preoperative, intraoperative, or postoperative (first 48 hours) administration of clonidine, dexmedetomidine, or mivazerol with controls were included. Studies had to report any of the following outcomes: mortality, myocardial infarction, ischemia, or supraventricular tachyarrhythmia. Treatment effects were calculated using the fixed-effects model. Heterogeneity was assessed using the Q test. **RESULTS:** Twenty-three trials comprising 3395 patients were included. Overall, alpha(2)-adrenergic agonists reduced mortality (relative risk [RR] = 0.64; 95% confidence interval [CI]: 0.42 to 0.99; P = 0.05) and ischemia (RR = 0.76; 95% CI: 0.63 to 0.91; P = 0.003) significantly. They also reduced mortality (RR = 0.47; 95% CI: 0.25 to 0.90; P = 0.02) and myocardial infarction (RR = 0.66; 95% CI: 0.46 to 0.94; P = 0.02) during vascular surgery. During cardiac surgery, alpha(2)-adrenergic agonists reduced ischemia (RR = 0.71; 95% CI: 0.54 to 0.92; P = 0.01) and were associated with trends toward lower mortality (RR = 0.49; 95% CI: 0.12 to 1.98; P = 0.3) and a reduced risk of myocardial infarction (RR = 0.83; 95% CI: 0.35 to 1.96; P = 0.7). **CONCLUSION:** Alpha-2 adrenergic agonists reduce mortality and myocardial infarction following vascular surgery. During cardiac surgery, they reduce ischemia and may also have effects on mortality and myocardial infarction. Large randomized trials are needed to evaluate these agents during cardiac and vascular surgery.

Publication Types: [Meta-Analysis](#)

Note: Clonidine oral 90 minutes preoperative 2.5-5 mcg/kg was the most common dose studied. Clonidine was used in 16/23 studies and dexmedetomidine in 6/23 studies.

PMID: 12829201

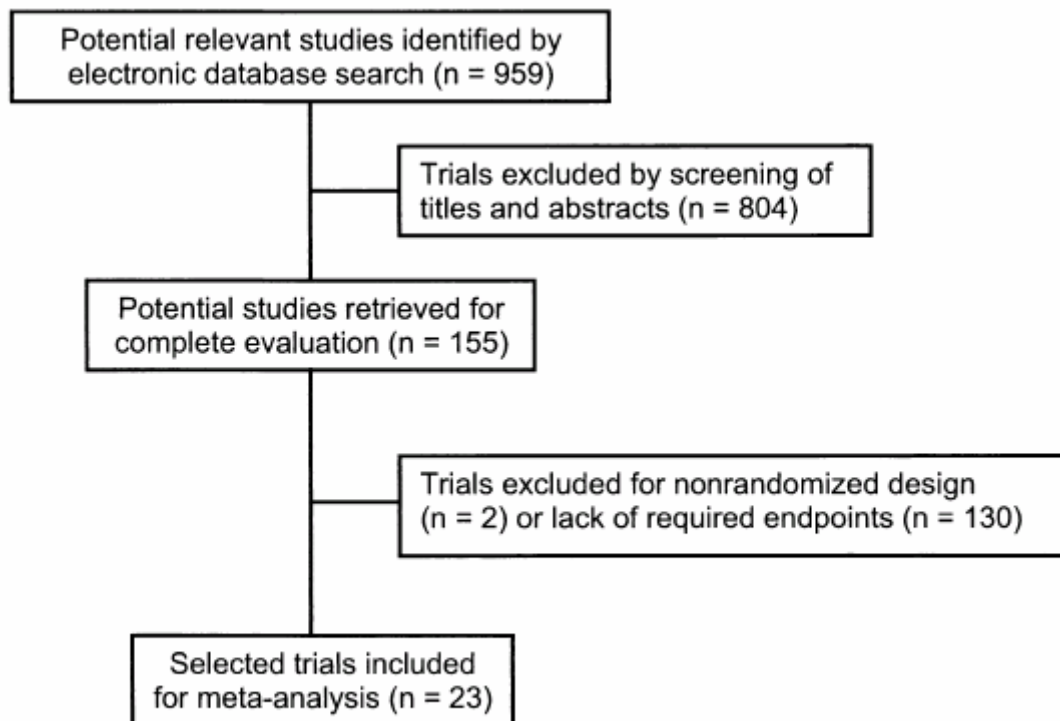


Figure 1. Flow diagram of meta-analysis.

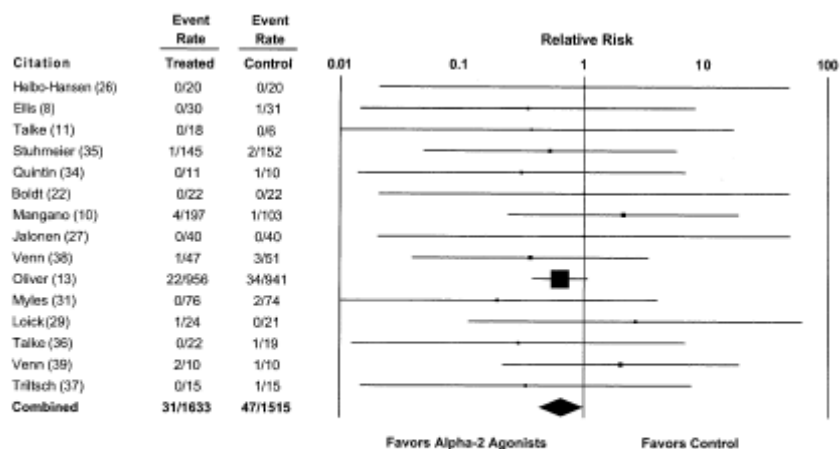


Figure 2. Effect of  $\alpha_2$ -agonists on mortality during all types of surgery, with a combined analysis of these results. Squares represent point estimates. The area of a square correlates with its contribution towards the weighted summary estimate. Horizontal lines denote 95% confidence intervals (CI), some of which extend beyond the limits of the scale. The overall effect, represented by the diamond, was a relative risk of 0.64 (95% CI: 0.42 to 0.99;  $P$  for heterogeneity = 0.92).

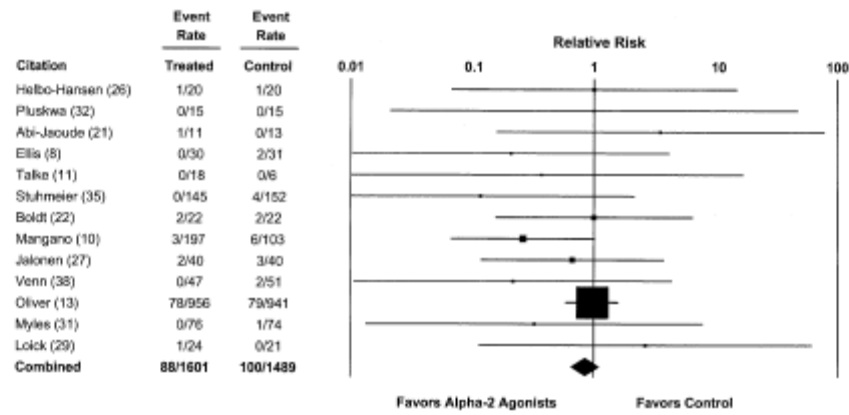


Figure 3. Effect of  $\alpha_2$ -agonists on myocardial infarction during all types of surgery, with a combined analysis of these results. Squares represent point estimates. The area of a square correlates with its contribution towards the weighted summary estimate. Horizontal lines denote 95% confidence intervals (CI), some of which extend beyond the limits of the scale. The overall effect, represented by the diamond, was a relative risk of 0.85 (95% CI: 0.65 to 1.11;  $P$  for heterogeneity = 0.55).

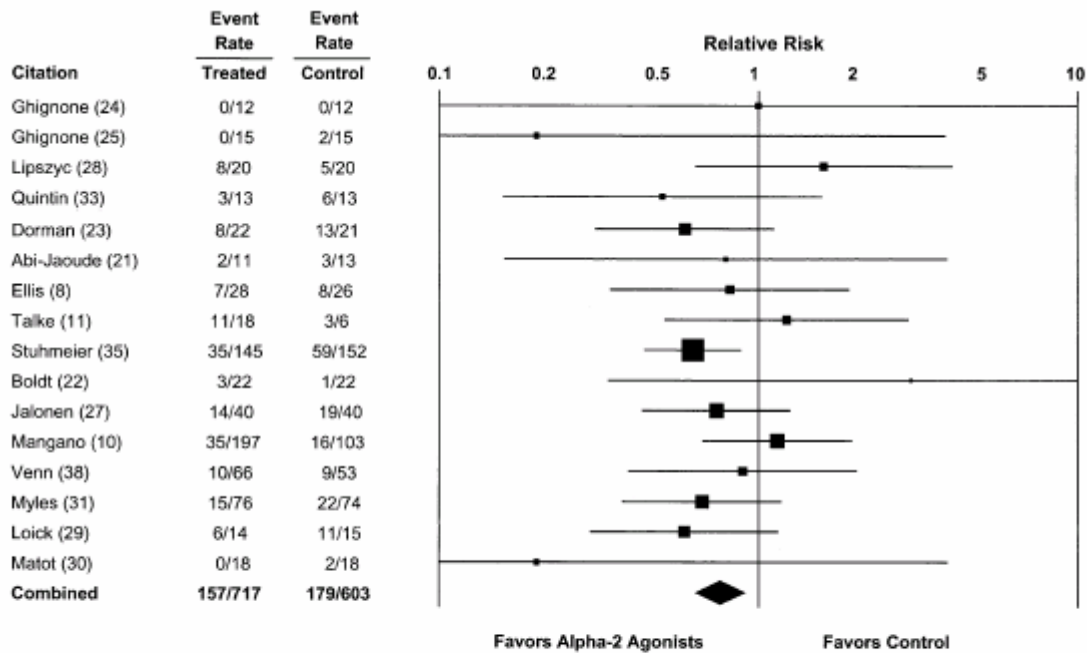


Figure 4. Effect of  $\alpha_2$ -agonists on myocardial ischemia during all types of surgery, with a combined analysis of these results. Squares represent point estimates. The area of a square correlates with its contribution towards the weighted summary estimate. Horizontal lines denote 95% confidence intervals (CI), some of which extend beyond the limits of the scale. The overall effect, represented by the diamond, was a relative risk of 0.76 (95% CI: 0.63 to 0.91;  $P$  for heterogeneity = 0.59).

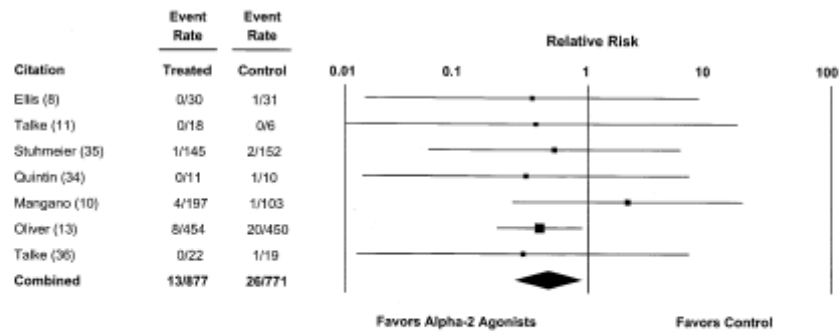


Figure 5. Effect of  $\alpha_2$ -agonists on mortality during vascular surgery, with a combined analysis of these results. Squares represent point estimates. The area of a square correlates with its contribution towards the weighted summary estimate. Horizontal lines denote 95% confidence intervals (CI), some of which extend beyond the limits of the scale. The overall effect, represented by the diamond, was a relative risk of 0.47 (95% CI: 0.25 to 0.90;  $P$  for heterogeneity = 0.82).

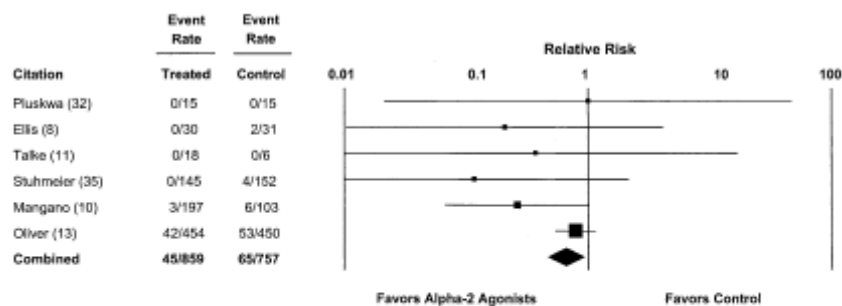


Figure 6. Effect of  $\alpha_2$ -agonists on myocardial infarction during vascular surgery, with a combined analysis of these results. Squares represent point estimates. The area of a square correlates with its contribution towards the weighted summary estimate. Horizontal lines denote 95% confidence intervals (CI), some of which extend beyond the limits of the scale. The overall effect, represented by the diamond, was a relative risk of 0.66 (95% CI: 0.46 to 0.94;  $P$  for heterogeneity = 0.21).

[Anaesth Intensive Care](#). 1999 Apr;27(2):137-47.

**Clonidine and cardiac surgery: haemodynamic and metabolic effects, myocardial ischaemia and recovery.**

[Myles PS](#), [Hunt JO](#), [Holdgaard HO](#), [McRae R](#), [Buckland MR](#), [Moloney J](#), [Hall J](#), [Bujor MA](#), [Esmore DS](#), [Davis BB](#), [Morgan DJ](#).

Department of Anaesthesia, Alfred Hospital, Melbourne, Victoria.

Clonidine may have beneficial effects in patients undergoing major surgery. We enrolled 156 patients having elective CABG surgery in a double-blind, randomized trial. Patients were randomized to receive either two doses of placebo (Group PP) or clonidine 5 micrograms/kg (Group CC). Perioperative measurements included haemodynamics, anaesthetic and analgesic drug usage, creatinine clearance, cortisol excretion, recovery times and quality of life (SF-36) after surgery. Overall, there was no significant difference with time to tracheal extubation (median [10-90 centile]): CC 7.1 (3.4-18) h vs PP 8.0 (4.3-17) h,  $P = 0.70$ ; but there was a higher proportion of patients extubated within four hours: CC 20% vs. PP 8%,  $P = 0.038$ . Clonidine resulted in a number of significant ( $P < 0.05$ ) haemodynamic changes, particularly pre-CPB: less tachycardia and hypertension, more bradycardia and hypotension. Clonidine was associated with a significant ( $P < 0.05$ ) reduction in anaesthetic drug usage, higher creatinine clearance, lower cortisol excretion and improvement in some aspects of quality of life. This study lends support to consideration of clonidine therapy in patients undergoing CABG surgery.

Publication Types:

- [Clinical Trial](#)
- [Randomized Controlled Trial](#)

PMID: 10212709 [PubMed - indexed for MEDLINE]

**Addition of dexmedetomidine to standard sedation regimens after cardiac surgery: an outcomes analysis.**

Dasta JF, Jacobi J, Sesti AM, McLaughlin TP.

College of Pharmacy, The Ohio State University, Columbus, Ohio 43210-1291, and the Department of Pharmacy, Clarian Health, Indianapolis, IN, USA.

**STUDY OBJECTIVE:** To characterize inpatient use of intravenous sedatives in the real-world setting, and to evaluate clinical and economic outcomes when dexmedetomidine was used with midazolam and propofol for select cardiovascular procedures. **DESIGN:** 12-month retrospective analysis. **DATA SOURCE:** An administrative claims database of operational data from a nationally representative sample of 250 medical and surgical hospitals. **PATIENTS:** Patients who received midazolam plus propofol (9996 patients) or dexmedetomidine, midazolam, plus propofol (356 patients) after cardiac valve or vessel surgery. **MEASUREMENTS AND MAIN RESULTS:** The source of patient demographics (e.g., age, sex, Charlson Comorbidity Index) and outcomes (e.g., charges, length of stay, mortality rate) was the hospital billing claim form. Patients in the dexmedetomidine-midazolam-propofol cohort tended to be younger and male and to have fewer comorbidities than those midazolam-propofol cohort. The primary outcomes for the three-drug cohort showed significant reductions in total charges/patient (approximately \$18,000,  $p < 0.05$ ), total hospital length of stay (0.6 days,  $p < 0.0001$ ), days in the intensive care unit or cardiac care unit (3.87 days,  $p < 0.0001$ ), and mortality (2%,  $p = 0.0142$ ). Although pharmacy charges were higher (approximately \$4000/patient), lower charges for the intensive care or cardiac care unit, operating room, room and board, and respiratory services were observed in the dexmedetomidine-midazolam-propofol cohort compared with the two-drug cohort. Also, mechanical ventilation was shorter by approximately 0.5 day in the three-drug cohort ( $p < 0.01$ ). **CONCLUSION:** These initial findings of a real-world assessment of dexmedetomidine use with other agents suggest favorable clinical and economic outcomes. Further research through randomized clinical trials of dexmedetomidine is warranted to better understand its optimum patient population, dosage, and the causality of the results, and to confirm the potential clinical and economic benefits observed in our patients.

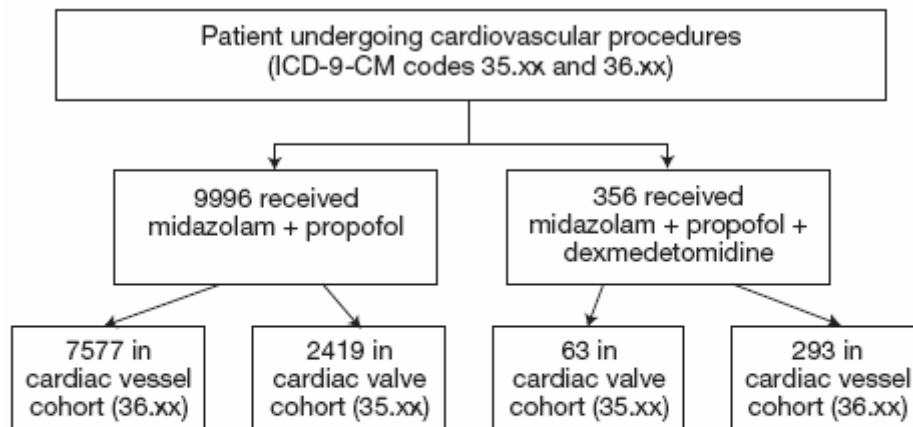
*Note*

*Study supported by Hospira, maker of Precedex.*

*Only 5% of the patients received dexmedetomidine as a single agent, most patients received midazolam and propofol too. Mortality outcomes were not adjusted for baseline risk of mortality. The patients in the dexmedetomidine group were younger, had lower baseline risk of mortality, and were from larger hospitals.*

*A metaanalysis has shown that clonidine, oral dose 5 mcg/kg 90 minutes before surgery, and other alpha 2 adrenergic agonists reduce mortality and cardiac ischemia and myocardial infarction in surgery patients.*

PMID: 16716133



**Figure 1.** Number of patients undergoing cardiac surgery defined by *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes in the sedative combination cohorts (i.e., midazolam + propofol, and dexmedetomidine + midazolam + propofol).

Table 1. Patient Characteristics in the Two-Drug and Three-Drug Cohorts

Characteristic	Midazolam + Propofol Cohort (n=9996)	Dexmedetomidine + Midazolam + Propofol Cohort (n=356)	p Value
	No. (%) of Patients		
Sex			<0.0001
Male	6755 (67.6)	281 (78.9)	
Female	3241 (32.4)	75 (21.1)	
Hospital size (no. of beds/facility)			<0.0001
1–299	1043 (10.4)	34 (9.6)	
300–399	4975 (49.8)	153 (43.0)	
400+	3951 (39.5)	169 (47.5)	
Unknown	27 (0.2)	0	
Region			<0.0001
East	3949 (39.5)	48 (13.5)	
North	2017 (20.2)	72 (20.2)	
South	3124 (31.3)	184 (51.7)	
West	879 (8.8)	52 (14.6)	
Unknown	27 (0.3)	0	
Patient admission source			<0.0001
Emergency room	1879 (18.8)	80 (22.5)	
Referral	1816 (18.2)	38 (10.7)	
Routine admission	3599 (36.0)	105 (29.5)	
Transfer from other facility	2026 (20.3)	82 (23.0)	
Other	676 (6.8)	51 (14.3)	
Charlson Comorbidity Index <sup>a</sup>			<0.05
0	3440 (34.4)	143 (40.2)	
1	5669 (56.7)	191 (53.7)	
2	764 (7.6)	16 (4.5)	
3	93 (0.9)	6 (1.7)	
4	30 (0.3)	0	
Mechanical ventilation or intubation	7806 (78.1)	348 (97.8)	<0.0001
Haloperidol administration	404 (4.0)	11 (3.1)	
Diagnosis of delirium	54 (0.5)	1 (0.3)	
	Mean ± SD		
Age (yrs)	65.6 ± 12.0	61.0 ± 11.1	<0.0001
Duration of mechanical ventilation or intubation (days)	5.46 ± 4.64	4.82 ± 3.38	<0.01

<sup>a</sup>A higher Charlson Comorbidity Index is indicative of a higher risk of mortality, with 0 indicating no comorbid illnesses and no increased risk of mortality, and 4 indicating presence of highest weighted and/or greatest number of comorbid illnesses, indicating highest risk of increased mortality.

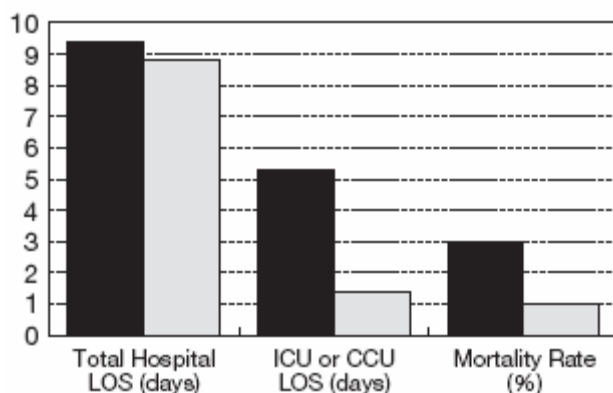


Figure 2. Mean total hospital length of stay (LOS), mean intensive care or cardiac care unit (ICU or CCU) LOS, and mortality rate for the study cohorts. Black bars represent midazolam and propofol cohort; gray bars represent dexmedetomidine, midazolam, and propofol cohort.

Table 2. Treatment Charges in the Two-Drug and Three-Drug Cohorts

Charge Category (ICD-9-CM code)	Midazolam + Propofol Cohort (n=9996)	Dexmedetomidine + Midazolam + Propofol Cohort (n=356)	p Value
Total charges (\$)	106,468 ± 85,033	88,678 ± 55,932	<0.05
Departmental charges (\$)			
Room and board (10–16x)	3035 ± 10,519	1517 ± 3425	<0.0001
Intensive care or cardiac care unit (20x, 21x)	17,694 ± 33,483	2761 ± 6439	<0.0001
Pharmacy (25x, 26x, 63x)	12,676 ± 15,914	16,674 ± 17,429	<0.0001
Medical and surgical supplies (27x, 62x)	19,843 ± 19,838	19,696 ± 15,472	NS
Laboratory (30x, 31x)	9318 ± 10,205	8346 ± 7319	<0.05
Radiology and nuclear medicine (32x, 33x, 34x)	1586 ± 2285	1628 ± 1817	NS
Operating room services (36x)	17,312 ± 15,086	12,834 ± 9321	<0.0001
Anesthesia (37x)	2521 ± 3411	3440 ± 1677	<0.0001
Blood, blood storage (38x, 39x)	2526 ± 4571	1892 ± 3120	<0.0001
Respiratory services (41x)	3086 ± 4792	2234 ± 3488	<0.0001
Pulmonary function (46x)	647 ± 1591	1062 ± 1630	<0.0001
Cardiology (48x)	5619 ± 8301	5522 ± 5322	NS
Electrocardiography (73x)	1045 ± 1522	1748 ± 1826	<0.0001
All other charges (\$)	7176 ± 24,013	7475 ± 13,792	NS

Data are mean ± SD.

Charge categories for which per patient average charge values were less than \$1000 are not displayed.

ICD-9-CM = *International Classification of Diseases, Ninth Revision, Clinical Modification*; NS = not significant.

## Dexmedetomidine does not improve patient satisfaction when compared with propofol during mechanical ventilation. (after CABG)

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**OBJECTIVE:** Dexmedetomidine (DEX) may provide a sedation level that enables sleep and communication, with less amnesia and pain medication requirements, during mechanical ventilation. *Our study directly assessed patient-perceived satisfaction with coronary artery bypass graft surgery after administration of DEX or propofol for intensive care unit (ICU) sedation.* **DESIGN:** Prospective, randomized clinical study with subsequent questionnaire administration. **SETTING:** Tertiary care surgical ICU. **PATIENTS:** A total of 89 adult, nonemergent, coronary artery bypass graft patients with an expected length of intubation of <24 hrs. **INTERVENTIONS:** Patients were randomized to either DEX or propofol; drug administration was performed via standardized anesthesia and nursing protocols. **MEASUREMENTS:** Patients reported perceptions of their ICU experience after mechanical ventilation with a modified numerical-scale Hewitt questionnaire, validated specifically for ICU patients. Patients were questioned regarding awareness, recall, generalized comfort, level of pain, ability to interact with healthcare providers and family, feelings of agitation and anxiety, perceived ease of extubation, ability to sleep or rest, and satisfaction with ICU experience. **MAIN RESULTS:** Groups were well matched at baseline, with a mean +/- sd age of 63.0 +/- 10.4 yrs and weight of 88.7 +/- 16.7 kg. *No difference was observed for length of surgery, length of intubation, or ICU stay (p > .05).* DEX patients perceived a shorter length of intubation (p = .044). *A deeper sedation level was found in the propofol group (p = .021), with similar morphine and midazolam requirements (p = .317).* Patient-rated level of overall awareness as a marker of amnesia did not differ between groups (p = .653). The ability to rest or sleep trended toward significance favoring propofol (p = .051). On evaluation of questionnaire ratings, DEX patients expressed more discomfort (p = .046), pain (p = .096), and sleeping difficulty (p = .036). Similar comfort levels were reported during extubation (p = .179).

**CONCLUSIONS:** *Despite theoretical advantages of DEX to improve overall patient satisfaction, the two agents provide similar responses to amnesia and pain control. According to our findings, DEX does not seem to have any advantage compared with propofol for short-term sedation after coronary artery bypass graft surgery.*

Publication Types: [Clinical Trial](#) [Randomized Controlled Trial](#)

PMID: 15891317

Table 1. Characteristics of postoperative coronary artery bypass graft patients

Characteristic <sup>a</sup>	Dexmedetomidine n = 43	Propofol n = 46	p Value
Male sex, n	35	38	.882
Age, yrs	63.6 ± 10.1	62.4 ± 10.7	.591
Weight, kg	88.0 ± 17.5	89.4 ± 16.0	.687
Length of anesthesia, hrs	4.53 ± 0.75	4.65 ± 0.693	.454
Length of surgery, hrs	3.19 ± 0.72	3.33 ± 0.63	.335
Length of mechanical ventilation, hrs	10.2 ± 12.8	8.97 ± 7.69	.589
Length of ICU stay, hrs <sup>b</sup>	23.0 (20.0–25.3)	23.0 (20.8–26.4)	.861
Baseline serum creatinine, mL/min	0.99 ± 0.24	1.11 ± 0.28	.037
Systolic blood pressure (highest), mm Hg	138 ± 17.4	135 ± 16.9	.483
Systolic blood pressure (lowest), mm Hg	79.1 ± 12.8	83.2 ± 10.0	.096
Mean arterial pressure (lowest), mm Hg	55.6 ± 7.06	57.6 ± 6.81	.181
Heart rate (highest), beats/min	91.0 ± 13.2	96.1 ± 16.7	.118
Heart rate (lowest), beats/min	68.1 ± 10.1	74.9 ± 11.2	.003
Central venous pressure (highest), mm Hg	14.0 ± 4.41	13.0 ± 4.95	.308
Central venous pressure (lowest), mm Hg	5.93 ± 3.25	5.83 ± 3.19	.879
ICU midazolam requirements, mg <sup>b</sup>	1.5 (0.5–2.5)	1.0 (0–3.0)	.317
ICU morphine requirements, mg <sup>b</sup>	6.0 (4.0–8.0)	6.0 (4.0–10)	.317
Alive at ICU discharge, %	98	100	.430

ICU, intensive care unit.

<sup>a</sup>All data expressed as mean ± SD unless otherwise specified; <sup>b</sup>data expressed as median (intra-quartile range).

Table 2. Patient-reported survey results (1 = best level, 10 = worst level)<sup>a</sup>

n = 89	Dexmedetomidine n = 43	Propofol n = 46	p Value
Baseline pain tolerance	6.5 (5.0–8.0)	6.0 (5.0–7.6)	.339
Overall comfort level	4.5 (1.0–8.4)	3.5 (1.3–5.0)	.243
Overall level of pain	5.0 (2.0–7.0)	3.5 (1.5–5.0)	.209
Communication			
Providers	3.0 (1.0–7.8)	3.3 (1.0–5.0)	.358
Family/friends	3.5 (1.3–7.5)	5.0 (1.0–8.0)	.724
How aware were you of your surroundings and what was happening?	6.0 (3.5–10)	5.8 (3.5–10)	.653
How easy was it to sleep?	3.8 (1.0–6.0)	3.0 (1.0–5.3)	.430
How comfortable was the extubation process?	3.0 (1.5–6.0)	5.0 (2.0–8.0)	.179
Rate how each of the following upset you			
Noise	1.0 (1.0–4.8)	2.0 (1.0–3.0)	.724
Handling and movement of various catheters and tubes	1.0 (1.0–4.5)	1.0 (1.0–2.5)	.536
Suctioning	2.0 (1.0–6.4)	2.5 (1.0–4.3)	.775
Difficulty resting or sleeping	5.0 (1.0–7.8)	2.0 (1.0–5.0)	.051
Inability to communicate by talking	4.5 (1.0–9.8)	3.0 (1.0–7.3)	.130
Rate how each of the following contributed to any difficulty experienced			
Pain	3.0 (1.0–6.0)	2.3 (1.0–5.0)	.209
Discomfort	3.5 (1.0–8.0)	3.8 (2.0–6.0)	.724
Noise	1.8 (1.0–4.9)	2.0 (1.0–4.0)	.880
Anxiety	2.5 (1.0–8.0)	2.5 (1.0–5.0)	.490
Being on the ventilator	2.5 (1.0–8.0)	2.8 (1.0–6.8)	.589
Insertion of catheters or tubes	1.5 (1.0–4.0)	2.0 (1.0–2.5)	.717
Fear of machine failure	1.0 (1.0–1.5)	1.0 (1.0–2.0)	.520

<sup>a</sup>All data expressed as median (intraquartile range).

[Anaesth Intensive Care](#). 2004 Dec;32(6):741-5.

## Dexmedetomidine infusion without loading dose in surgical patients requiring mechanical ventilation: haemodynamic effects and efficacy.

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We investigated the haemodynamic effects and the efficacy of a continuous infusion of dexmedetomidine without a loading dose in 50 patients having had cardiac surgery (n = 33), complex major surgery (n = 9) and multiple trauma (n = 8). The mean age was 60 (+/- 16) years, and the mean APACHE II score was 13 (+/- 5). Dexmedetomidine was commenced at an initial rate of 0.2 to 0.4 microg/kg/h (depending on whether anaesthetic or sedative agents had already been used) and rescue analgesia and sedation was administered with morphine and midazolam respectively. Propofol was used if additional sedation was needed. Sedation was targeted to a modified Motor Activity Assessment Score. Eighty percent of patients required no or "minimal" rescue therapy (< 10 mg midazolam/day and/or < 10 mg morphine/day and/or < 100 mg propofol/day). The cardiac surgery group needed the least rescue therapy. A statistically significant but clinically unimportant reduction in mean heart rate and mean systolic blood pressure was observed over the first six hours (P < 0.0001, and P = 0.009 respectively). The baseline heart rate of 85 (+/- 17) beats per minute (bpm), fell to a low of 78 (+/- 13) bpm at four hours and then remained stable throughout the infusion period. The systolic blood pressure fell from 125 (+/- 22) mmHg to a low of 112 (+/- 20) mmHg at 1.5 hours with minimal change afterwards. Dexmedetomidine was an effective sedative and analgesic in this group of complex surgical and trauma patients with pronounced benefit in the cardiac surgery group. Omitting the loading dose avoided undesirable haemodynamic effects without compromising sedation and analgesia. PMID: 15648981

## **ICU sedation after coronary artery bypass graft surgery: dexmedetomidine-based versus propofol-based sedation regimens.**

[Herr DL](#), [Sum-Ping ST](#), [England M](#).

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**OBJECTIVE:** To compare dexmedetomidine-based to propofol-based sedation after coronary artery bypass graft (CABG) surgery in the intensive care unit (ICU). **DESIGN:** Randomized, open label. **SETTING:** Twenty-five centers in the United States and Canada. **PARTICIPANTS:** Two hundred ninety-five adults undergoing CABG surgery. **INTERVENTIONS:** At sternal closure, patients in group A received 1.0 microg/kg of dexmedetomidine over 20 minutes and then 0.2 to 0.7 microg/kg/h to maintain a Ramsay sedation score  $>$  or  $=$  3 during assisted ventilation and  $>$  or  $=$  2 after extubation. Patients could be given propofol for additional sedation if necessary; group B patients received propofol-based care according to each investigator's standard practice. **MEASUREMENTS AND MAIN RESULTS:** *Mean sedation levels were within target ranges in both groups and were not significantly different. Median times to weaning and extubation (410 min dex, 462 propofol) were similar, although fewer dexmedetomidine patients remained on the ventilator beyond 8 hours.* Morphine use was significantly reduced in the dexmedetomidine group. Only 28% of the dexmedetomidine patients required morphine for pain relief while ventilated versus 69% of propofol-based patients ( $p < 0.001$ ). Propofol patients required 4 times the mean dose of morphine while in the ICU. Mean blood pressure increased initially in both groups, then decreased to 3 mmHg below baseline in dexmedetomidine patients; mean arterial pressure remained at 9 mmHg above baseline in propofol patients. Hypertension and hypotension occurred more frequently in the dexmedetomidine group. No ventricular tachycardia occurred in the dexmedetomidine-sedated patients compared with 5% of the propofol patients ( $p = 0.007$ ). Respiratory rates and blood gases were similar. Fewer dexmedetomidine patients received beta-blockers ( $p = 0.014$ ), antiemetics ( $p = 0.015$ ), nonsteroidal anti-inflammatory drugs ( $p < 0.001$ ), epinephrine ( $p = 0.030$ ), or high-dose diuretics ( $p < 0.001$ ). **CONCLUSION:** Dexmedetomidine provided safe and effective sedation for post-CABG surgical patients and significantly reduced the use of analgesics, beta-blockers, antiemetics, epinephrine, and diuretics.

Publication Types: [Clinical Trial](#) , [Multicenter Study](#) , [Randomized Controlled Trial](#)

PMID: 14579210

### Note:

- If a dexmedetomidine-sedated patient could not be maintained within the desired sedation range and if the infusion rate was already at the recommended maximum of 0.7 mcg/kg/h, the patient could be given propofol. By this criterion, 16 of 148 (11%) dexmedetomidine patients received propofol at some point during assisted ventilation at an average rate of 19 mg/hour.
- Hypertension occurred significantly more frequently in the dexmedetomidine group (19 incidents in 18 patients  $v$  6 events in 6 propofol patients,  $p = 0.018$ ) Greater than 60% (12/19) of these incidents in the dexmedetomidine group occurred within the first 2 hours after start of the infusion; 4 occurred within the first 30 minutes (loading dose duration was 20 minutes).
- The most frequent adverse event in both groups was hypotension, 24% in the dexmedetomidine group versus 16% in the propofol group ( $p = 0.111$ ). In the dexmedetomidine group, 26% (11/43) of these events occurred within the first hour, most of them during or within 10 minutes after the loading infusion. Four incidents were listed as severe (3, dexmedetomidine; 1, propofol). One incident in each group was considered serious, moderate in intensity, life threatening, or medically important but not related to study drug. Hypovolemia was concurrent with hypotension in more dexmedetomidine patients (19%, 7/36) than propofol patients (8%, 2/24).

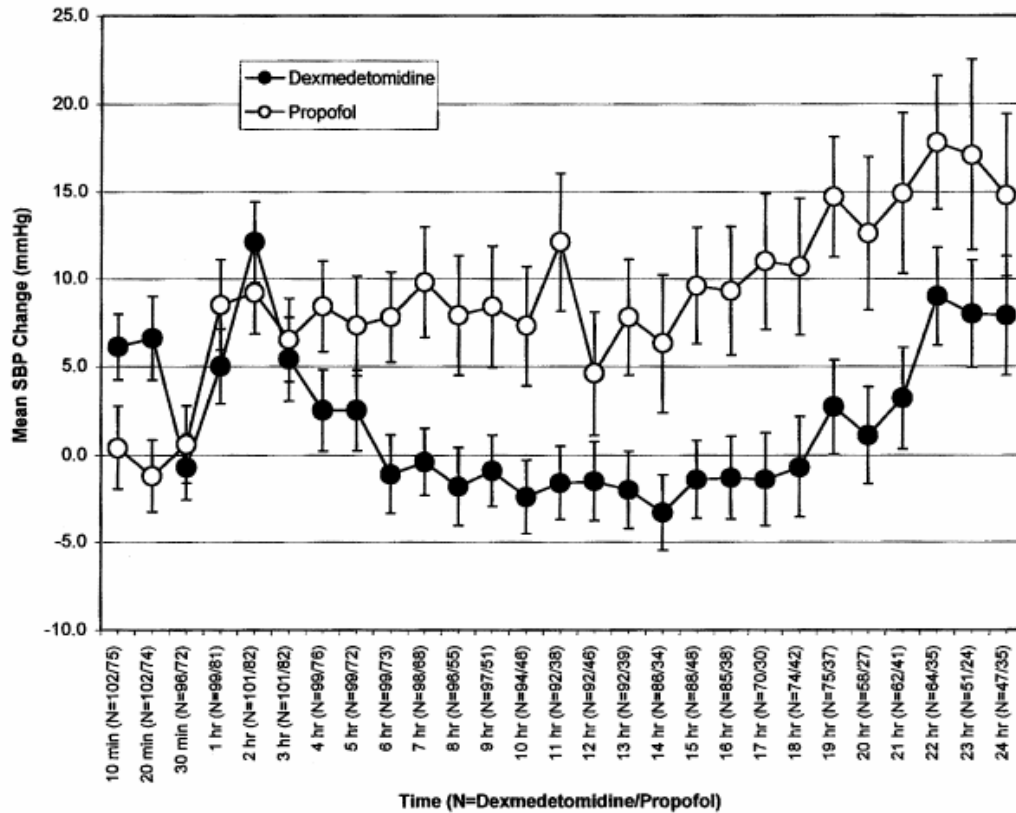


Fig 2. Change from baseline in mSBP. Dexmedetomidine, closed circles; propofol-based, open circles. Lines above and below each point represent standard error of the means. Y-axis zero is baseline (mean SBP for each treatment group just before sternal closure). Points represent the mean change from baseline in mmHg. Blood pressures were recorded every 10 minutes after sternal closure, then hourly up to 24 hours. Time points shown are relative to the start of study drug infusion at sternal closure. The number of patients still receiving study drug (or still in the ICU, in the case of propofol) are indicated along the x-axis. As the study progressed, fewer patients remained in the ICU.

DEXMEDETOMIDINE AFTER CABG SURGERY

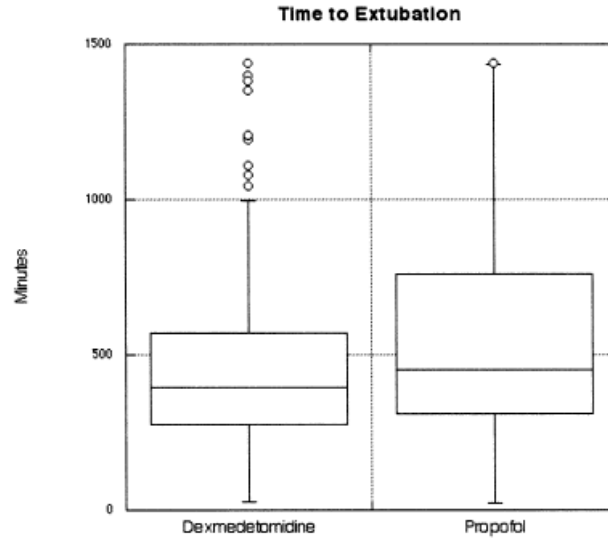


Fig 1. Times to extubation by treatment box and Whisker plot. The y-axis indicates elapsed time in minutes between sternal closure and when each patient was ready for extubation. Each box represents the interquartile distance enclosing 50% of the patients between quartile 1 (25th percentile) and quartile 3 (75th percentile), with the median value shown as a horizontal line within the box. The line extending from the bottom of each box includes data points for <25% of each group to their respective minimum extubation times (28 minutes and 25 minutes, dexmedetomidine and propofol, respectively). The 90th percentile limit is indicated by a short horizontal line above each box. The open circles represent discrete time points for the remaining 10% of patients. Eleven dexmedetomidine patients are represented in 9 circles, 3 at the highest circle at 1,440 minutes (the default time for patients who were on the ventilator at 24 hours).

**Table 4. Incidence (≥3%) of Treatment-Emergent Adverse Events**

	Dexmedetomidine	Propofol Based	p Value*
Total number of patients	148	147	
Patients reporting at least 1 adverse event n (%)	105 (71)	98 (67)	0.453
Hypotension	36 (24)	24 (16)	0.111
Nausea	22 (15)	19 (13)	0.737
Hypertension†	18 (12)	6 (4)	0.018
Hypovolemia	15 (10)	9 (6)	0.287
Atelectasis	14 (9)	12 (8)	0.838
Atrial fibrillation	12 (8)	12 (8)	>0.999
Fever	11 (7)	7 (5)	0.467
Hemorrhage	8 (5)	9 (6)	0.809
Pleural effusion	7 (5)	12 (8)	0.246
Vomiting	7 (5)	5 (3)	0.770
Hypocalcemia	7 (5)	4 (3)	0.541
Anemia	6 (4)	7 (5)	0.785
Dry mouth	6 (4)	1 (<1)	0.121
Hypoxia	6 (4)	6 (4)	>0.999
Pulmonary edema	6 (4)	4 (3)	0.750
Rigors	5 (3)	4 (3)	>0.999
Bradycardia	5 (3)	2 (1)	0.448
Tachycardia	5 (3)	5 (3)	>0.999
Agitation	5 (3)	1 (<1)	0.214
Confusion	5 (3)	1 (<1)	0.214
Bronchospasm	5 (3)	5 (3)	>0.999
Pneumothorax	5 (3)	2 (1)	0.448
Oliguria	5 (3)	7 (5)	0.572
Blood pressure fluctuation	4 (3)	1 (<1)	0.371
Hyperglycemia	4 (3)	5 (3)	0.750
Myocardial infarction	4 (3)	1 (<1)	0.371
Pain	4 (3)	1 (<1)	0.371
Pericarditis	4 (3)	4 (3)	>0.999
Cardiac failure	3 (2)	4 (3)	0.723
Peripheral edema	2 (1)	4 (3)	0.448
Acidosis	2 (1)	6 (4)	0.173
Tachycardia ventricular†	0 (0)	7 (5)	0.007

NOTE. Adverse event terms from World Health Organization-Adverse Reaction Term definitions. Events are organized by decreasing frequency in the dexmedetomidine group. A patient who reported 2 or more different adverse events in the same body system would be counted only once.

\*By Fisher exact test.

†Statistically significant difference between groups.

[J Intensive Care Med.](#) 2003 Jan-Feb;18(1):29-41

### The role of the alpha2-adrenoceptor agonist dexmedetomidine in postsurgical sedation in the intensive care unit

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Dexmedetomidine was evaluated for sedation of 401 post-surgical patients in this double-blind, randomized, placebo-controlled, multicenter trial. Dexmedetomidine or saline was started on arrival in the intensive care unit (ICU) (1.0 mcg/kg for 10 minutes), then titrated at 0.2 to 0.7 mcg/kg/h to effect. Patients could be given propofol if necessary. Morphine was administered for pain. Sixty percent of the dexmedetomidine patients required no other sedative to maintain an RSS > or = 3; 21% required < 50 mg propofol. In contrast, 76% of the control group received propofol; 59% required > or = 50 mg. During assisted ventilation, both groups were sedated to similar levels (3.4 dexmedetomidine, 3.1 control group). Dexmedetomidine patients required significantly less morphine for pain relief (4.09 mg Dex versus 8.46 mg control P <.001). Times to extubation were similar 471.5 min and 498 minutes for dex and control respectively. Dexmedetomidine and control groups had no discernable differences in effect on respiratory rate, oxygen saturation, duration of weaning, or times to extubation. Nurses judged the dexmedetomidine patients were easier to manage. Later, fewer dexmedetomidine patients remembered pain (23% dex versus 34% control) or discomfort (33% dex versus 37% control). The majority of dexmedetomidine patients maintained blood pressures within normal range, without rebound. Hypertension (12% dex,

23% control), atelectasis (< 1% dex, 5% control), and rigors (< 1% dex, 4% control) occurred more frequently in the control group, while hypotension (30% dex, 10% control), severe hypotension (5% dex, 2% control) and bradycardia (9% dex, 2% control) occurred more frequently in the dexmedetomidine group. Preoperative cardiovascular conditions were not risk factors for dexmedetomidine patients.

PMID: 15189665 [PubMed - indexed for MEDLINE]

**Table 4.** Propofol Administered

	Dexmedetomidine	Control	P Value
During assisted ventilation			
n	203	198	
Total dose (mg)	71.6 ± 17.51	513.2 ± 55.6	< .001
n <sup>a</sup>	198	195	
Mean rate (mg/h)	8.6 ± 1.9	65.6 ± 6.8	< .001
During study drug administration			
n	203	198	
Total dose (mg)	80.0 ± 21.3	559.8 ± 60.5	< .001
Mean rate (mg/h)	5.3 ± 1.2	39.1 ± 4.1	< .001

Values are expressed as mean total dose ± SEM. The P values are from an analysis of variance.

a. Exact time of extubation missing for 5 dexmedetomidine patients and 3 control patients.

**Table 5.** Nursing Assessments and Patient Management Index

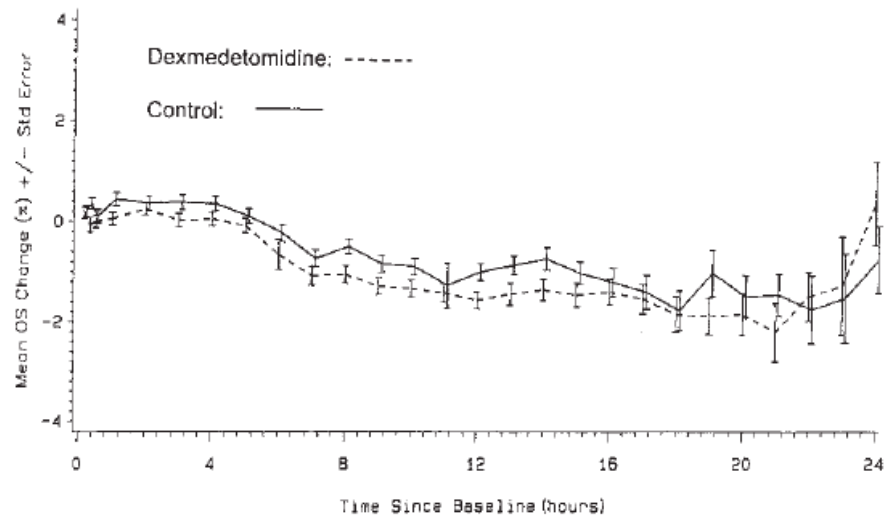
	Dexmedetomidine		Control	
	n	Score	n	Score
Overall sedation and tolerance of the intensive care unit <sup>a</sup>	180	1.5 ± 0.04	176	1.9 ± 0.06
Tolerance of endotracheal tube/ventilator <sup>b</sup>	180	1.3 ± 0.03	175	1.5 ± 0.04
Ease of communication with patient <sup>c</sup>	179	2.1 ± 0.07	176	2.4 ± 0.08
Ease of management of the patient <sup>b</sup>	178	1.2 ± 0.03	175	1.6 ± 0.05
Patient Management Index <sup>d</sup>	177	6.1 ± 0.12	174	7.3 ± 0.18

a. 1 = *very easy*, 2 = *easy*, 3 = *moderate*, 4 = *difficult*.

b. 1 = *good*, 2 = *moderate*, 3 = *poor*.

c. 1 = *very easy*, 2 = *easy*, 3 = *moderate*, 4 = *difficult*, 5 = *not possible*.

d. The P value from the Cochran-Mantel-Haenszel row mean score statistic adjusted for center differences was < .001.

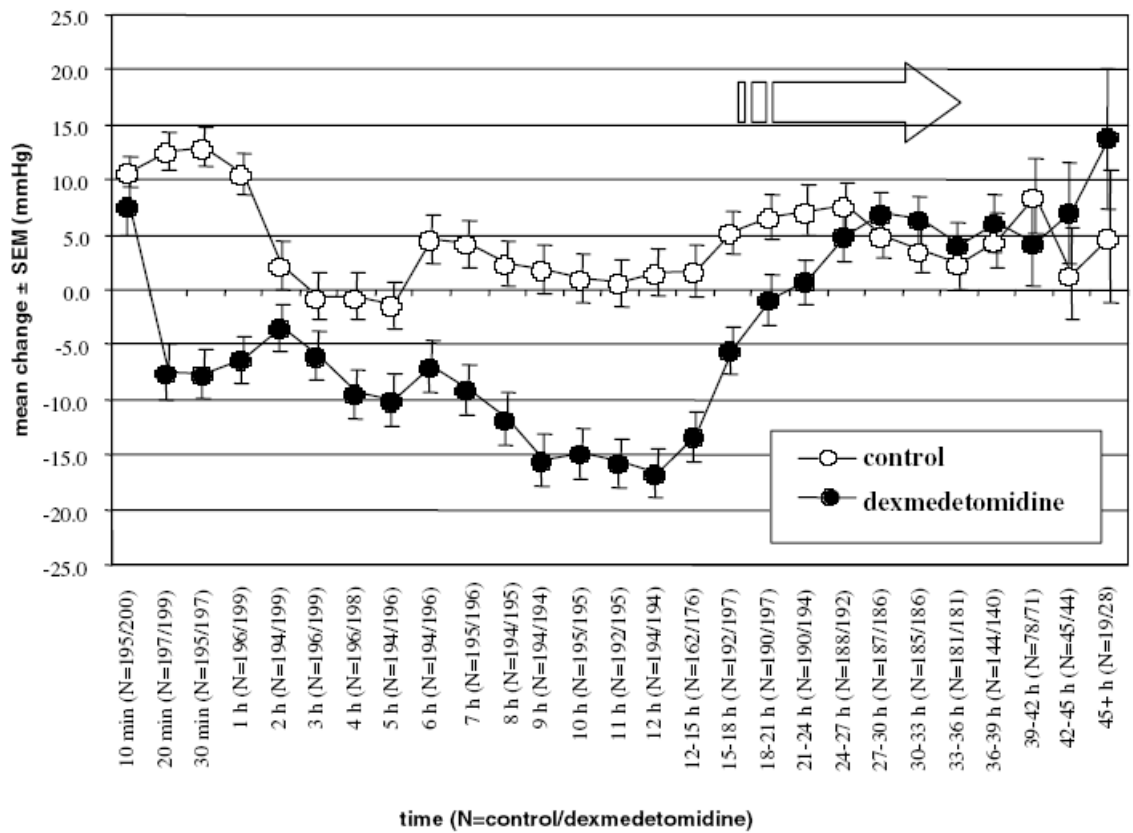


**Fig 2.** Mean change from baseline for oxygen saturation while receiving study drug. Control group values are offset +6 minutes for comparison of standard error bars. Baseline in the dexmedetomidine group was 98.7% and in the control group was 98.5%.

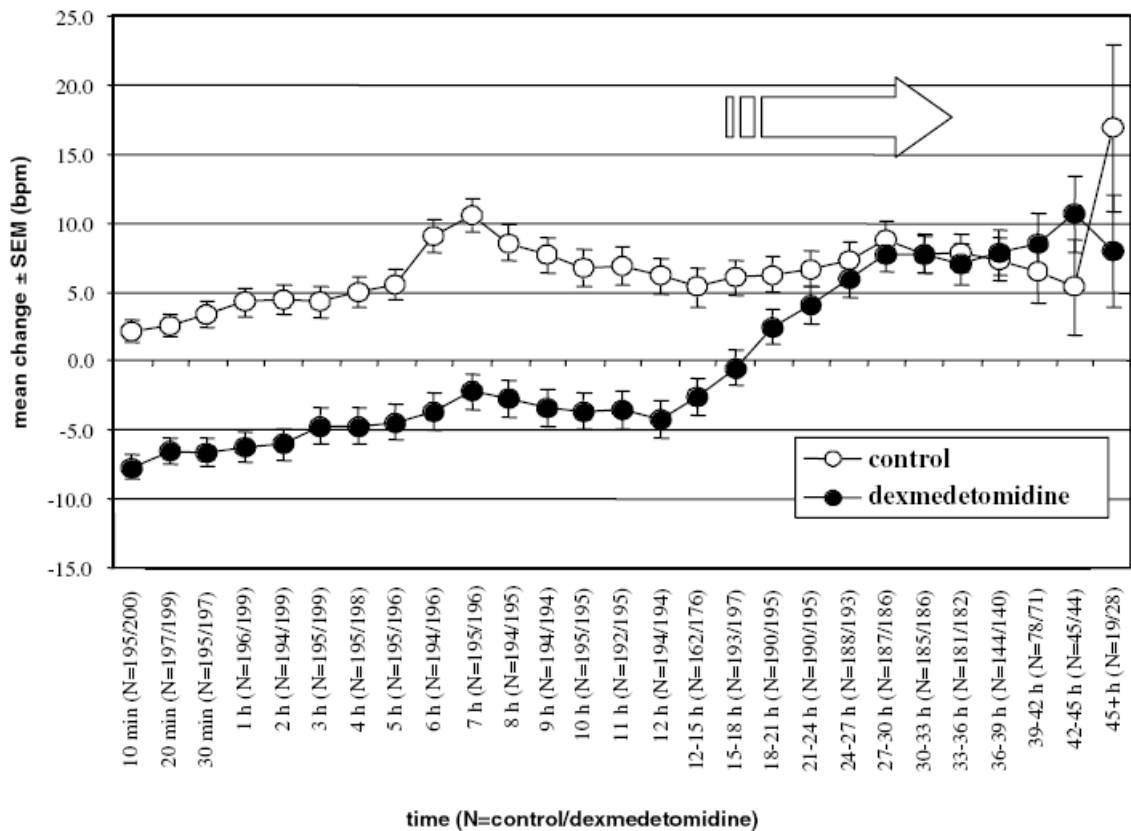
**Table 6.** Most Common Treatment-Emergent Adverse Events

All Treated Patients	Dexmedetomidine (n = 203)	Control (n = 198)	P Value
Patients with at least 1 treatment-emergent adverse event	121 (60%)	112 (57%)	.545
Hypotension	61 (30%)	20 (10%)	< .001
Hypertension	24 (12%)	45 (23%)	.005
Nausea	22 (11%)	19 (10%)	.743
Bradycardia	18 (9%)	4 (2%)	.003
Vomiting	10 (5%)	11 (6%)	.826
Hypoxia	8 (4%)	5 (3%)	.575
Mouth dry	7 (3%)	1 (< 1%)	.068
Fever	6 (3%)	7 (4%)	.785
Tachycardia	4 (2%)	6 (3%)	.539
Hemorrhage	3 (1%)	7 (4%)	.216
Atrial fibrillation	3 (1%)	5 (3%)	.499
Acidosis	3 (1%)	5 (3%)	.499
Confusion	3 (1%)	6 (3%)	.333
Agitation	2 (< 1%)	6 (3%)	.171
Atelectasis	1 (< 1%)	9 (5%)	.010
Rigors	1 (< 1%)	8 (4%)	.019

Adverse events experienced by  $\geq 3\%$  of patients in either group. *P* values were calculated by Fisher's Exact Test. Terms are from the World Health Organization-Adverse Reaction Terms.



**Fig 3.** Mean change from baseline in systolic blood pressure during the entire study period. This figure includes all randomized intent-to-treat patients, whether still receiving study drug or not. N equals the number of control/dexmedetomidine patients with data available at each time point. Study drug was stopped after 12 hours for most patients (large dashed arrow). Vital signs were collected at 3-hour intervals for another 24 hours after study drug infusions were stopped. By hour 16, study drug had been stopped for approximately two thirds of the patients in both groups.



**Fig 4.** Mean change from baseline in heart rate for all patients during and after study drug. This figure includes all patients for 48 hours after the start of study drug (same population as in Fig 3). The large dashed arrow begins at the point where study protocol minimums were fulfilled. After 12 hours, study drug had been stopped for most patients. Baseline mean heart rate in the dexmedetomidine group was 80.8 bpm and in the control group was 79.8 bpm. N equals the number of placebo/dexmedetomidine patients whose data were included at each time point.

Bispectral index-guided sedation with dexmedetomidine in intensive care: a prospective, randomized, double blind, placebo-controlled phase II study.

[Triltsch AE](#), [Welte M](#), [von Homeyer P](#), [Grosse J](#), [Genahr A](#), [Moshirzadeh M](#), [Sidiropoulos A](#), [Konertz W](#), [Kox WJ](#), [Spies CD](#). *Crit Care Med*. 2002 May;30(5):1007-14

Department of Anesthesiology and Intensive Care Medicine, Benjamin Franklin Medical Center, Free University of Berlin, Germany. **OBJECTIVE:** To compare dexmedetomidine vs. placebo with respect to the amount of additional propofol and morphine used for bispectral index-guided sedation and analgesia in mechanically ventilated, intensive care patients after surgery. **DESIGN:** Prospective, randomized, double blind, placebo-controlled, phase II clinical trial. **SETTING:** General surgical and cardiac surgical intensive care units. **PATIENTS:** Thirty patients scheduled for major surgery requiring mechanical ventilation for a minimum of 6 hrs were included in the study. **INTERVENTIONS:** Patients were assigned randomly to receive either dexmedetomidine (loading infusion, 1.0 microg/kg over 10 mins; maintenance infusion, 0.1-0.7 microg x kg(-1) x hr(-1)) or placebo after intensive care unit admission. **MEASUREMENTS AND MAIN RESULTS:** Sedation was guided by using the electroencephalographic parameter bispectral index, a new noninvasive method to estimate the level of sedation. We aimed at maintaining bispectral index ranges between 60 and 70 during mechanical ventilation before starting weaning, 65 and 95 during weaning, and 85 to 95 postextubation. Additional sedative and analgesic medication was given (propofol and morphine) as clinically indicated and within the previously mentioned bispectral index ranges. Patients receiving dexmedetomidine required significantly less propofol during mechanical ventilation (0.87 +/- 0.21 vs. 1.52 +/- 0.30 mg/kg/hr; p <.01) and weaning (0.17 +/- 0.06 vs. 0.62 +/- 0.21 mg/kg/hr; p <.001) to maintain the target bispectral index range. There was no difference in morphine dose requirements in the dexmedetomidine group compared with placebo. Hemodynamic stability during weaning and after extubation was better maintained in patients receiving dexmedetomidine. **CONCLUSIONS:** Dexmedetomidine reduced propofol requirements and improved hemodynamic stability during bispectral index-guided intensive care unit sedation.

PMID: 12006795 [PubMed - indexed for MEDLINE]

[Anesthesiology](#). 2002 Sep;97(3):592-8.

## **Autonomic nervous system responses during sedative infusions of dexmedetomidine.**

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**BACKGROUND:** The purpose of this study was to determine the effects of dexmedetomidine on systemic and cardiac autonomic reflex responses during rest and during thermal stress. **METHODS:** Volunteers received either placebo or low- or high-dose dexmedetomidine (target plasma concentrations 0.3 or 0.6 ng/ml, respectively) infusions in a prospectively randomized, double-blinded crossover study design. After 1 h, baroreflex sensitivity was assessed, and then core body temperature was raised to the sweating threshold and then lowered to the shivering threshold. Plasma catecholamines and blood pressure were measured, and cardiac autonomic responses were assessed by analysis of heart rate variability. **RESULTS:** Compared with placebo, plasma norepinephrine concentrations, blood pressure, heart rate, and some heart rate variability measures were lower after 1-h infusion of dexmedetomidine, but baroreflex responses did not differ significantly. Dexmedetomidine blunted the systemic and cardiac sympathetic effects of sweating observed during placebo infusion but had no effect on parasympathetic measures. Increases in blood pressure, and systemic catecholamines due to shivering were observed during placebo and dexmedetomidine, but these responses were less with dexmedetomidine. During shivering, dexmedetomidine infusion was associated with higher low-frequency and high-frequency heart rate variability power but lower heart rate compared with the sweating threshold and with the control period, suggesting nonreciprocal cardiac autonomic responses. **CONCLUSIONS:** Infusion of dexmedetomidine results in compensated reductions in systemic sympathetic tone without changes in baroreflex sensitivity. Dexmedetomidine blunts heart rate and the systemic sympathetic activation due to sweating, but it is less effective in blunting cardiac sympathetic responses to shivering. During dexmedetomidine infusion, cardiac sympathetic and parasympathetic tone may have nonreciprocal changes during shivering.

Publication Types: [Clinical Trial](#) , [Randomized Controlled Trial](#)

PMID: 12218525

[Anaesth Intensive Care](#). 1995 Oct;23(5):543-7.

## **Effect of propofol infusion on the endocrine response to cardiac surgery.**

[NG A](#), [Tan SS](#), [Lee HS](#), [Chew SL](#).

Department of Anaesthesia and Intensive Care, Singapore General Hospital.

The effect of propofol infusion on the stress response was studied in patients undergoing coronary artery bypass graft (CABG). Ten patients received propofol infusion during cardiopulmonary bypass (CPB) and ten controls received diazepam. Blood levels of cortisol, adrenaline and noradrenaline were sampled. There was a significant reduction in all three hormones ( $P < 0.05$ ) in the study group. In addition, the amount of sodium nitroprusside used during CPB was significantly reduced ( $P < 0.05$ ), 1.1 versus 9.7 mg, propofol versus control group respectively.

Publication Types: [Clinical Trial](#) [Randomized Controlled Trial](#)

PMID: 8787251

[Anesth Analg](#). 2002 Aug;95(2):461-6, table of contents.

## **The efficacy, side effects, and recovery characteristics of dexmedetomidine versus propofol when used for intraoperative sedation.**

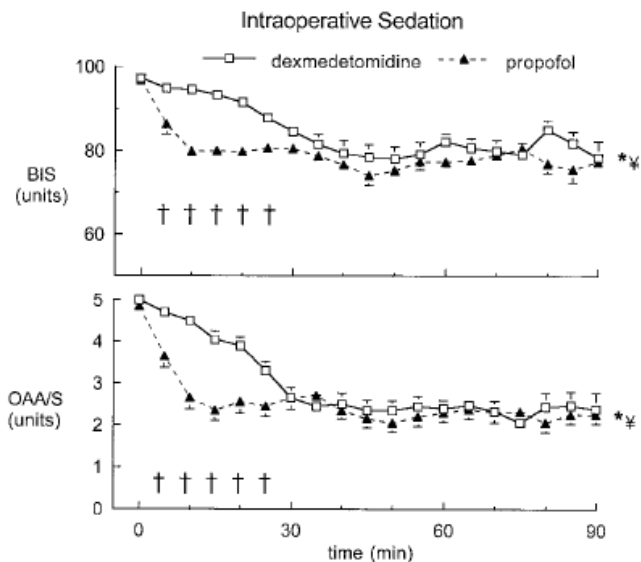
[Arain SR](#), [Ebert TJ](#).

Department of Anesthesiology, Medical College of Wisconsin and VA Medical Center, Milwaukee, Wisconsin, USA.

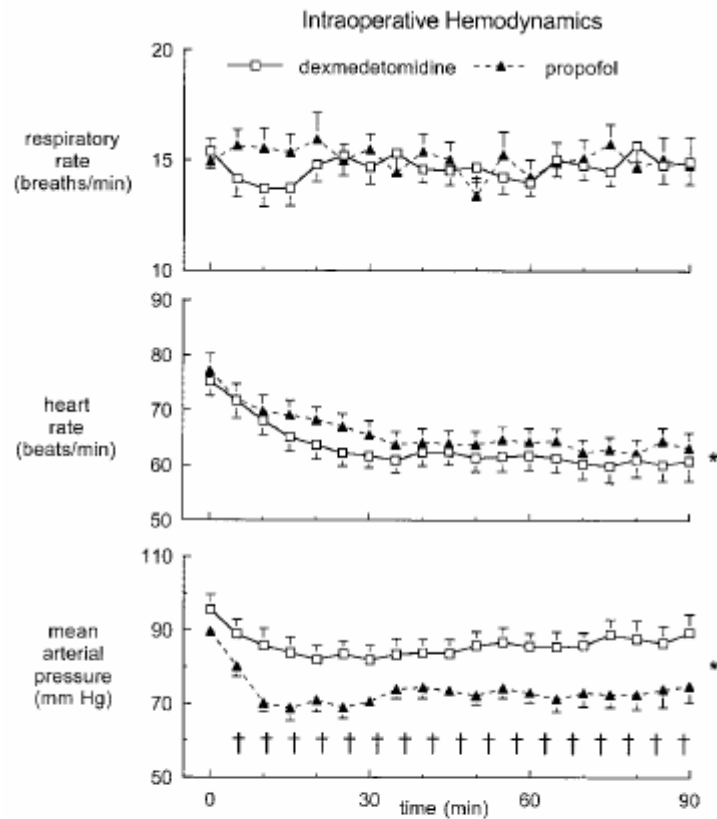
We evaluated the cardio-respiratory effects of equi-sedative doses of dexmedetomidine and propofol for intraoperative sedation, on patients undergoing hernia repair or orthopedic procedures. Secondary comparison end points were time to achieve and terminate sedation and postoperative analgesia and psychomotor performance. Forty patients scheduled for elective surgery provided informed consent and were randomized equally to receive either dexmedetomidine (1 microg/kg initial loading dose for 10 min; maintenance, 0.4-1 microg. kg(-1). h(-1)) or propofol (75 microg. kg(-1). min(-1) x 10 min; maintenance, 12.5-75 microg. kg(-1). min(-1)). Hemodynamic variables (heart rate and mean arterial blood pressure), sedation (visual analog scale and Observer Assessment of Alertness/Sedation), bispectral index score of sedation, ventilation (respiratory rate, O2 sat, and ETCO2), psychomotor performance (digital symbol substitution test), and pain (visual analog scale) were determined during surgery and up to 95 min after surgery. Intraoperative sedation levels were targeted to achieve a bispectral index score of 70-80. Patient demographics, ASA class, surgical procedure, and baseline cardio-respiratory variables were similar between groups. Patients receiving propofol did not have significant respiratory depression. *Sedation was achieved more rapidly after initiating infusions with propofol (10 minutes) versus dexmedetomidine (25 minutes).* The average infusion rate for dexmedetomidine was 0.7 microg. kg(-1). h(-1) and 38 microg. kg(-1). min(-1) for propofol. There were no differences between groups in psychomotor performance and respiratory rate during recovery. All patients maintained clinically normal oxygen saturation and Etco2 concentrations. *MAP was significantly reduced during the intraoperative period by propofol and the reduction was significantly less in patients receiving dexmedetomidine.* During recovery dexmedetomidine patients had significantly smaller needs for morphine and were significantly more sedated than propofol patients. In

recovery previous use of dexmedetomidine resulted in more sedation, lower blood pressure, and improved analgesia (less morphine use). IMPLICATIONS: Dexmedetomidine may be useful for perioperative sedation. It has a slower onset and offset of sedation compared with propofol. Dexmedetomidine was associated with improved analgesia and less morphine use in the postoperative period.

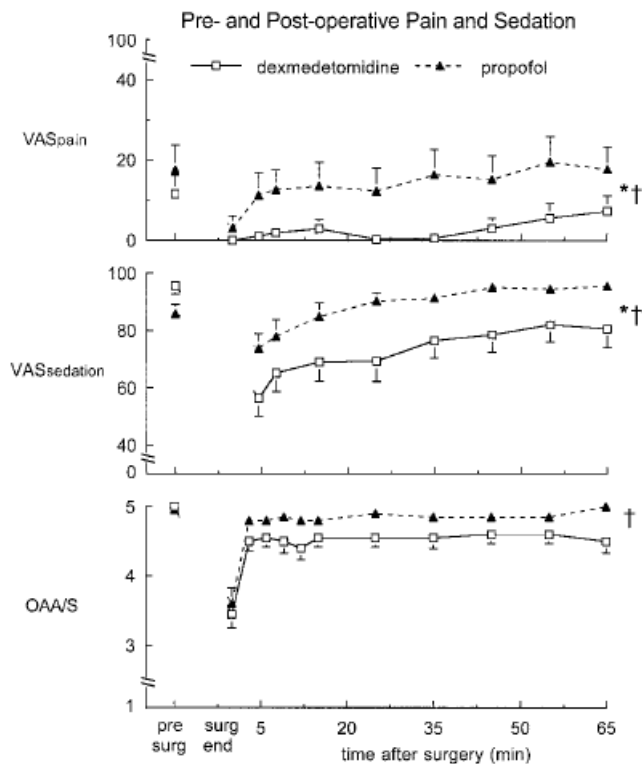
Publication Types: [Clinical Trial](#) , [Randomized Controlled Trial](#)  
 PMID: 12145072



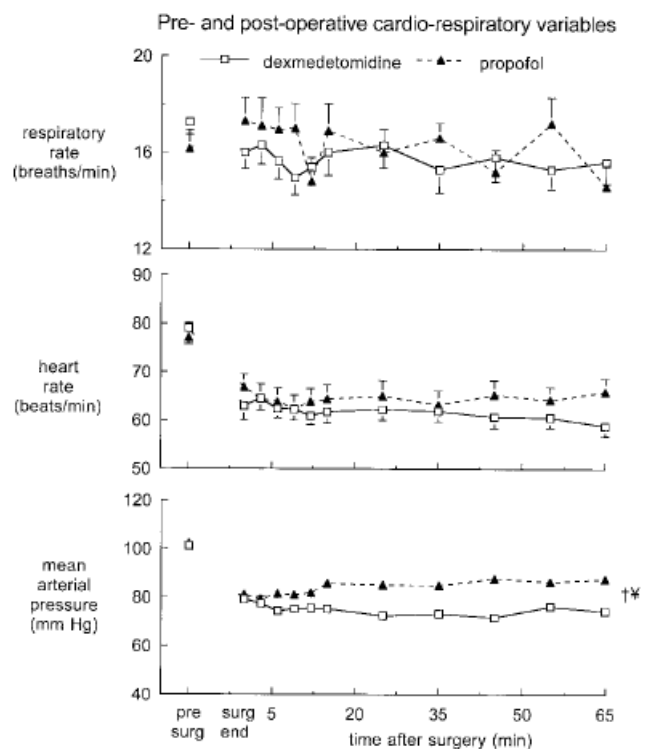
**Figure 1.** Targeted sedation during the intraoperative period. Objective (bispectral index score [BIS]) and subjective (Observer Assessment of Alertness/Sedation [OAA/S]) measures of sedation were more rapidly achieved during the intraoperative period when using propofol. \*Difference over time compared with baseline values ( $P < 0.05$ ); †Difference between dexmedetomidine and propofol; ‡Significant interaction (different response between drugs over time).



**Figure 2.** Cardio-respiratory variables during the intraoperative period. Respiratory rate was maintained at baseline levels throughout surgery in both groups. Heart rate (HR) decreased from baseline similarly for both groups. Immediately and throughout surgery, propofol sedation was associated with lower blood pressures than similarly sedated patients receiving dexmedetomidine. \*Difference over time compared with baseline values ( $P < 0.05$ ); †Difference between dexmedetomidine and propofol.



**Figure 4.** Pain and sedation scores from the pre- and postoperative period. Visual analog scale for pain (VASpain) was taken in the holding area and at fixed intervals throughout the recovery period. Initially, on entering the recovery room, there was no pain in either treatment group because of the unresolved regional anesthetic that was given for the surgical procedure. Thereafter, pain scores were significantly lower in the group that had received dexmedetomidine during the surgical procedure. Both the Observer Assessment of Alertness/Sedation (OAA/S) and the VAS sedation indicated a significantly greater degree of sedation with the use of dexmedetomidine. \*Difference over time compared with baseline values ( $P < 0.05$ ); †Difference between dexmedetomidine and propofol.



**Figure 5.** Cardio-respiratory variables from the pre- and postoperative period. Respiratory rate was unchanged from the presurgery rate at all recovery time points. Postoperative heart rates (HRs) were lower in the recovery period but did not differ between groups. Mean arterial blood pressure (MAP) also was lower in the postoperative period, and previous use of dexmedetomidine was associated with significantly lower MAP than the propofol-treated patients. \*Difference over time compared with baseline values ( $P < 0.05$ ); †Difference between dexmedetomidine and propofol; ‡Significant interaction (different response over time).

slightly opposed by direct  $\alpha_2$ -mediated vasoconstriction.

[Br J Anaesth](#). 2001 Nov;87(5):684-90.

## Comparison between dexmedetomidine and propofol for sedation in the intensive care unit: patient and clinician perceptions.

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Department of Anaesthesia & Intensive Care, Worthing Hospital, West Sussex, UK.

The  $\alpha_2$  agonist dexmedetomidine is a new sedative and analgesic agent which is licensed in the USA for post-operative intensive care sedation. We compared dexmedetomidine with propofol in patients requiring sedation in intensive care. Twenty adult patients expected to require a minimum of 8 h artificial ventilation after surgery (abdominal or pelvic) were randomized to receive sedation with either dexmedetomidine or propofol infusions on arrival to ICU. Additional analgesia, if required, was provided by an alfentanil infusion. Depth of sedation was monitored using both the Ramsay sedation score (RSS) and the bispectral index (BIS).

Cardiovascular, respiratory, biochemical and haematological data were obtained. Patients' perceptions of their intensive care stay were assessed using the Hewitt questionnaire. Sedation was equivalent in the two groups [median (interquartile range): RSS, propofol group 5 (4-5), dexmedetomidine group 5 (4-6) ( $P=0.68$ ); BIS, propofol group 53 (41-64), dexmedetomidine group 46 (36-58);  $P=0.32$ ]. The percentage of time spent at an ideal depth of sedation (RSS 2-4) was similar: 49.1% for propofol and 46.3% for dexmedetomidine group. The propofol group received three times more alfentanil compared with patients sedated with dexmedetomidine [2.5 (2.2-2.9)  $\text{mg h}^{-1}$  versus 0.8 (0.65-1.2)  $\text{mg h}^{-1}$  ( $P=0.004$ )]. No differences were found in arterial pressures between the groups, but heart rate was significantly lower in the dexmedetomidine group [mean (SD) 75 (6) vs 90 (4)  $\text{beats min}^{-1}$ ]. The median dexmedetomidine infusion rate was 0.86 (0.45-1.06)  $\text{mcg/kg/hour}$ , no data provided for propofol. Extubation times were similar and rapid with the use of both sedative agents [median (range) 28 (20-50) and 29 (15-50) min ( $P=0.63$ ) respectively for the propofol and dexmedetomidine

*groups*]. No adverse events related to the sedative infusions occurred in either group. Despite ventilation and intubation, patients sedated with dexmedetomidine could be easily roused to cooperate with procedures (e.g. physiotherapy, radiology) without showing irritation. From the clinician's and patient's perspectives, dexmedetomidine is a safe and acceptable sedative agent for those requiring intensive care. The rate pressure product is reduced in patients receiving dexmedetomidine, which may protect against myocardial ischaemia. Dexmedetomidine reduces the requirement for opioid analgesia.

Publication Types: [Clinical Trial](#) ,[Randomized Controlled Trial](#)

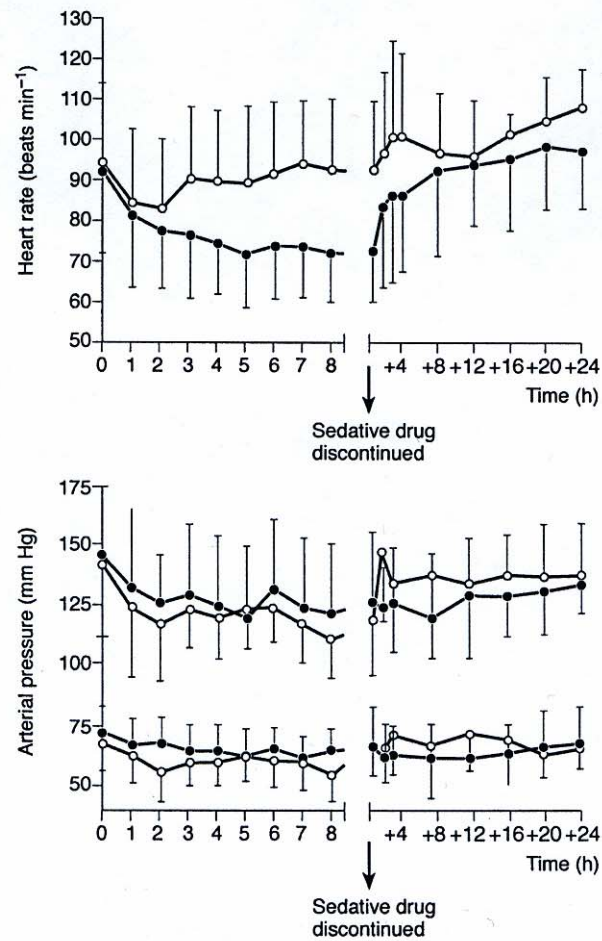
Two patients died 14 and 17 days after recovery from surgery in dexmedetomidine group and one died 35 days after recovery from surgery in the propofol group (no other info about the deaths were available from the paper)

A separate paper below addressed adrenocortical function, endocrine and inflammatory responses looked at in this study.

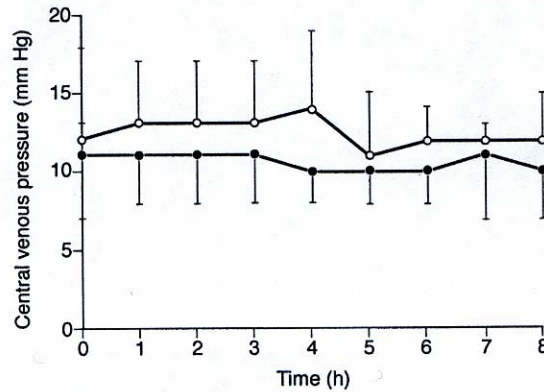
No sig. Differences were found between the two drugs with central venous pressure.

Abbott laboratories has contributed to the research fund for this study.

PMID: 11878517



**Fig 2** Mean (SD) heart rate (beats min<sup>-1</sup>) and systolic and diastolic arterial blood pressures (mm Hg) in the dexmedetomidine (closed circles) and propofol (open circles) groups for the first 8 h of intubation and after sedative drug discontinuation. The heart rates were significantly lower in the dexmedetomidine group during intubation ( $P=0.034$  and  $0.15$  during and after sedative infusion respectively). There were no differences in systolic and diastolic blood pressures between the two groups ( $P=0.60$  during and after sedative infusion).  $n=10$  in both groups except at 7 and 8 h whilst intubated, when  $n=8$  and  $n=7$  in the dexmedetomidine and propofol groups respectively.



**Fig 3** Mean (SD) central venous pressure (mm Hg) in the dexmedetomidine (closed circles) and propofol (open circles) groups for the first 8 h of intubation. There were no significant differences between the two variables at any time point ( $P=0.21$ ).  $n=10$  in both groups except at 7 and 8 h, when  $n=8$  and  $n=7$  in the dexmedetomidine and propofol groups respectively.

**Table 2** Mean (SD) mechanical ventilation variables and arterial blood gases for the first 8 h period of intubation and mechanical ventilation in patients sedated with dexmedetomidine (D) and propofol (P).  $n=10$  in both groups except at 8 h, when  $n=8$  and  $n=7$  in the dexmedetomidine and propofol groups respectively. RR = respiratory rate; TV = tidal volume;  $P_{max}$  = maximum airway pressure; PEEP = positive end-expiratory pressure;  $P_{aCO_2}$  arterial  $PCO_2$ ;  $P_{aO_2}/F_{iO_2}$  = arterial/inspired oxygen ratio; BE = base excess. \* $P=0.003$ ; propofol vs dexmedetomidine group at that time point

	Baseline		2 h		4 h		6 h		8 h	
	D	P	D	P	D	P	D	P	D	P
RR ( $min^{-1}$ )	13 (1)	14 (2)	14 (1)	14 (1)	14 (2)	14 (2)	13 (3)	14 (2)	14 (3)	14 (3)
TV (ml)	579 (122)	624 (102)	596 (91)	619 (111)	606 (95)	640 (152)	622 (111)	585 (89)	599 (154)	635 (111)
$P_{max}$ (cm $H_2O$ )	24 (3)	25 (3)	25 (3)	25 (3)	25 (3)	25 (3)	24 (3)	24 (2)	24 (3)	25 (2)
PEEP (cm $H_2O$ )	5 (1)	7 (3)	5 (1)	7 (3)	5 (1)	6 (2)	5 (1)	6 (1)	5 (1)	6 (1)
pH	7.32 (0.10)	7.36 (0.07)	7.35 (0.06)	7.33 (0.11)	7.37 (0.08)	7.33 (0.08)	7.38 (0.08)	7.33 (0.10)	7.39 (0.08)	7.34 (0.04)
$P_{aCO_2}$ (kPa)	4.9 (0.9)	5.2* (0.3)	4.6 (0.4)	5.8* (1.0)	4.7 (0.6)	5.6* (1.2)	4.5 (0.4)	5.8* (1.5)	4.6 (0.8)	5.6* (0.3)
$P_{aO_2}/F_{iO_2}$	43 (13)	29 (14)	45 (12)	38 (14)	50 (14)	33 (11)	45 (8)	32 (8)	42 (12)	37 (10)
BE	-6 (4)	-3 (4)	-5 (4)	-4 (3)	-4 (3)	-3 (3)	-4 (4)	-3 (3)	-4 (3)	-3 (3)

**Table 3** Mean (SD) biochemical and haematological variables at baseline and 24 and 48 h after commencement of the study in the dexmedetomidine and propofol groups. There were significant within-group differences in sodium, urea and creatinine concentrations for the dexmedetomidine group and in the leucocyte count for the propofol group over the 48 h study period. Significant within-group differences were also present in the platelet counts for both groups ( $P<0.01$ ). PTT = prothrombin ratio; KCCT = kaolin cephalin clotting time. \* $P<0.05$ ; \*\* $P<0.01$  compared with baseline

	Dexmedetomidine			Propofol			P value (between groups)
	Baseline	24 h	48 h	Baseline	24 h	48 h	
<b>Biochemical variables</b>							
Na (mmol $litre^{-1}$ )	138 (4)	142 (4)*	143 (3)**	140 (3)	142 (3)	142 (5)	0.84
K (mmol $litre^{-1}$ )	4.7 (0.9)	4.2 (0.4)	4.0 (0.5)	4.2 (0.4)	4.4 (0.5)	4.4 (0.5)	0.85
Urea (mmol $litre^{-1}$ )	5.0 (2.6)	6.3 (2.5)	8.0 (4.1)*	5.2 (2.7)	5.9 (4.8)	6.7 (5.3)	0.78
Creatinine ( $\mu$ mol $litre^{-1}$ )	86 (20)	99 (38)	113 (48)*	83 (22)	97 (35)	101 (40)	0.68
Bilirubin ( $\mu$ mol $litre^{-1}$ )	27 (36)	28 (41)	21 (28)	12 (5)†	16 (12)	16 (11)	0.37
Alanine aminotransferase (IU $litre^{-1}$ )	23 (17)	26 (25)	26 (30)	38 (48)	46 (71)	47 (71)	0.93
Alkaline phosphatase (IU $litre^{-1}$ )	87 (113)	38 (19)	46 (28)	55 (31)	39 (22)	53 (18)	0.64
Albumin (g $litre^{-1}$ )	24 (14)	18 (7)	18 (6)	24 (11)	17 (7)	21 (6)	0.67
Calcium (mmol $litre^{-1}$ )	2.10 (0.20)	2.09 (0.19)	2.08 (0.19)	2.08 (0.20)	1.97 (0.19)	1.98 (0.19)	0.27
Phosphate (mmol $litre^{-1}$ )	1.25 (0.18)	1.22 (0.32)	1.07 (0.36)	1.12 (0.49)	1.27 (0.48)	1.17 (0.43)	0.95
<b>Haematological variables</b>							
Haemoglobin (g $dL^{-1}$ )	11.3 (1.4)	10.8 (0.9)	10.5 (0.6)	11.9 (2.2)	10.9 (0.8)	11.3 (0.9)	0.21
Leucocytes ( $\times 10^9$ $litre^{-1}$ )	8.1 (1.9)	13.0 (10.0)	12.7 (5.4)	8.9 (2.9)	9.3 (2.9)	11.3 (2.4)*	0.44
Platelets ( $\times 10^9$ $litre^{-1}$ )	239 (88)	160 (59)**	160 (84)**	208 (64)	151 (77)**	155 (68)**	0.63
PTT	1.0 (0.2)	1.2 (0.2)	1.2 (0.2)	1.0 (0.2)	1.1 (0.2)	1.1 (0.2)	0.13
KCCT (s)	47 (7)	48 (3)	51 (7)	48 (9)	55 (9)	47 (5)	0.67
Thrombin time (s)	13 (2)	12 (2)	12 (2)	13 (3)	16 (6)	13 (1)	0.34

## Effects of dexmedetomidine on adrenocortical function, and the cardiovascular, endocrine and inflammatory responses in post-operative patients needing sedation in the intensive care unit.

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Note: This is the same patients study in the article above.

We have compared the effects of dexmedetomidine and propofol on endocrine, metabolic, inflammatory and cardiovascular responses in patients in the intensive care unit (ICU) after major surgery (abdominal or pelvic). Twenty patients who were expected to require 8 h of post-operative sedation and ventilation were allocated randomly to receive either an infusion of dexmedetomidine 0.2-2.5 microg kg(-1) h(-1) or propofol 1-3 mg kg(-1) h(-1) on arrival to ICU. Arterial pressure, heart rate and sequential concentrations of circulating cortisol, adrenocorticotrophic hormone (ACTH), growth hormone, prolactin, insulin, glucose and interleukin 6 were measured. An ACTH stimulation test was performed in all patients who received dexmedetomidine. Heart rate was significantly lower in the dexmedetomidine patients. There were no differences in arterial pressure, cortisol, ACTH, prolactin and glucose concentrations between the two groups. A positive response to the ACTH stimulation test varied depending on the diagnostic criteria used. The insulin concentration was significantly lower in the dexmedetomidine group at 2 h (P=0.021), although this did not affect blood glucose concentrations. Growth hormone concentrations were significantly higher in dexmedetomidine-treated patients overall (P=0.036), but circulating concentrations remained in the physiological range. Interleukin 6 decreased in the dexmedetomidine group. We conclude that dexmedetomidine infusion does not inhibit adrenal steroidogenesis when used for short-term sedation after surgery.

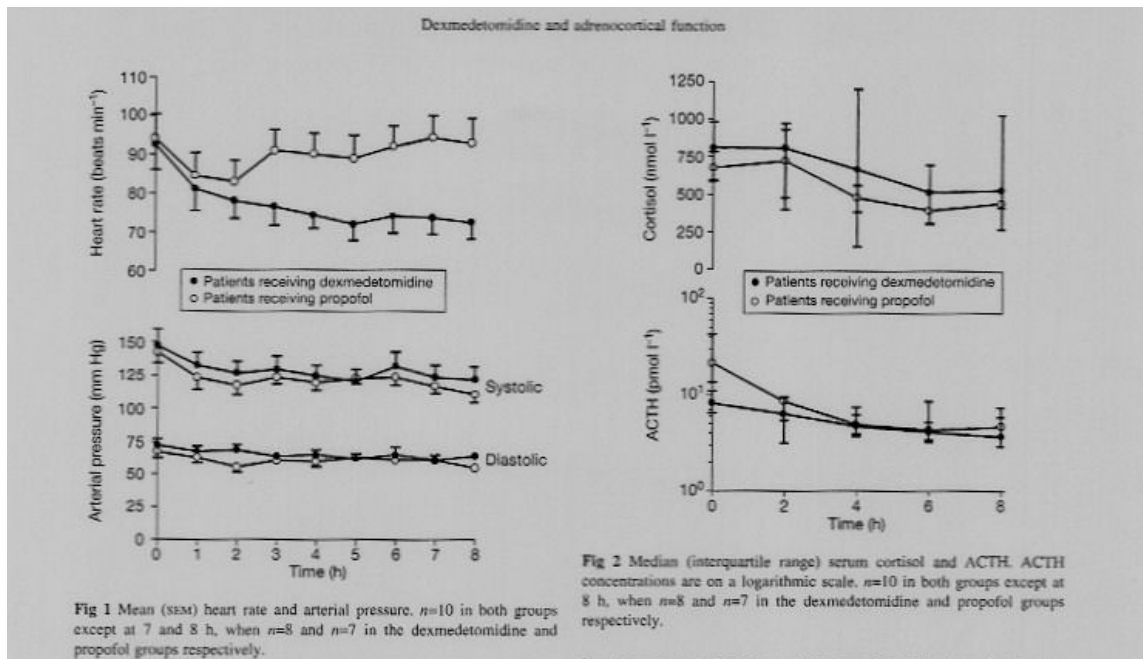
Publication Types: [Clinical Trial](#), [Randomized Controlled Trial](#)

PMID: 11575340

No dexmedetomidine patients had a serum cortisol < 138 nmol/L, but 2 propofol patients did. There were no differences in the cortisol (P=0.22) and ACTH (P=0.74) between propofol and dexmedetomidine. Cortisol concentration <400 or <500nmol/L were found in 6 and 7 patients with dexmedetomidine and in 7 and 9 patients propofol infusion. Of the dexmedetomidine patients 5 failed the third ACTH analysis method (difference between pre and post was >200, of these 4 of these had high normal basal cortisol concentrations), 2 failed the second ACTH analysis method (peak cortisol >550), 1 patient failed all three (including 1<sup>st</sup> method of peak cortisol >400)

Abbott laboratories has contributed to the research fund for this study.

At conc > 10<sup>-6</sup> of dexmedetomidine, cortisol synthesis is inhibited in animals. Therapeutic levels are <10<sup>-9</sup>.



**Table 2** Assessment of adrenocortical function using three different criteria to interpret the short ACTH stimulation test in patients who had received dexmedetomidine infusions. +=pass, -=fail

Patient	Total dexmedetomidine dose ( $\mu\text{g kg}^{-1}$ )	Method 1: peak cortisol $>400 \text{ nmol litre}^{-1}$	Method 2: peak cortisol $>550 \text{ nmol litre}^{-1}$	Method 3: cortisol incremental rise $>200 \text{ nmol litre}^{-1}$
1	12.6	+	+	+
2	6.4	+	+	-
3	6.2	+	+	-
4	5.4	+	+	+
5	14.8	+	+	+
6	12.8	+	-	-
7	12.9	+	+	+
8	11.4	-	-	-
9	8.2	+	+	-
10	10.3	+	+	+

**Table 3** Median (interquartile range) blood glucose, serum insulin, prolactin, GH and IL-6 concentrations in patients infused with dexmedetomidine (D) or propofol (P). D vs P refers to between-group differences determined by estimation of the area under the curve. There was a significant difference in insulin concentrations between the groups at 2 h ( $P=0.021$ ),  $n=10$  in both groups except at 8 h, when  $n=8$  and  $n=7$  in the dexmedetomidine and propofol groups respectively for all measurements, apart from insulin, when  $n=7$  and  $n=6$  respectively

		Baseline	2 h	4 h	6 h	8 h	D vs P
Glucose ( $\text{mmol litre}^{-1}$ )	D	6.8 (6.1-7.0)	6.1 (5.7-8.6)	7.4 (6.1-8.7)	7.6 (6.0-8.0)	6.3 (5.9-7.9)	$P=0.22$
	P	6.9 (5.6-7.7)	7.1 (6.4-7.8)	6.8 (6.1-7.7)	7.0 (6.0-7.5)	6.5 (6.0-7.5)	
Insulin ( $\text{mU litre}^{-2}$ )	D	0.15 (0-0.15)	0* (0-3.7)	3.7 (0-4.4)	4.0 (0-4.7)	0.15 (0-13.0)	$P=0.12$
	P	10.6 (5.7-15.2)	10.4* (4.6-15.7)	10.9 (2.9-17.5)	12.0 (2.9-17.5)	8.2 (3-17.2)	
Prolactin ( $\text{mU litre}^{-1}$ )	D	352 (177-464)	196 (135-480)	120 (79-391)	192 (135-332)	205 (101-438)	$P=0.25$
	P	488 (308-603)	413 (287-485)	321 (218-524)	318 (207-385)	405 (176-423)	
GH ( $\text{mU litre}^{-1}$ )	D	4.3 (3.0-5.8)	6.4 (2.9-10.0)	8.7 (4.9-13.6)	7.8 (4.3-10.5)	8.4 (4.4-9.8)	$P=0.04$
	P	1.5 (1.0-2.2)	0.9 (0-1.4)	0.6 (0-1.1)	1.4 (0-3.9)	3.5 (0.8-5.1)	
IL-6 ( $\text{pg ml}^{-2}$ )	D	404 (232-595)	385 (354-526)		301 (162-369)	249 (165-354)	$P=0.36$
	P	286 (178-524)	251 (149-478)		388 (208-428)	527 (461-700)	

Anesth Analg. 2001 Nov;93(5):1205-9.

## The pharmacokinetics of dexmedetomidine in volunteers with severe renal impairment.

[De Wolf AM](#), [Fragen RJ](#), [Avram MJ](#), [Fitzgerald PC](#), [Rahimi-Danesh F](#).

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Dexmedetomidine, an alpha2-adrenergic agonist with sedative and analgesic properties, is mainly cleared by hepatic metabolism. Because the pharmacokinetics of dexmedetomidine have not been determined in humans with impaired renal function, we studied them in volunteers with severe renal disease and in control volunteers. Six volunteers with severe renal disease and six matched volunteers with normal renal function received dexmedetomidine, 0.6 microg/kg, over 10 min. Venous blood samples for the measurement of plasma dexmedetomidine concentrations were drawn before, during, and up to 12 h after the infusion. Two-compartmental pharmacokinetic models were fit to the drug concentration versus time data. We also determined its hemodynamic, respiratory, and sedative effects. There was no difference between Renal Disease and Control groups in either volume of distribution at steady state ( $1.81 \pm 0.55$  and  $1.54 \pm 0.08 \text{ L/kg}$ , respectively; mean  $\pm$  SD) or elimination clearance ( $12.5 \pm 4.6$  and  $8.9 \pm 0.7 \text{ mL} \times \text{min}^{-1} \times \text{kg}^{-1}$ , respectively). However, elimination half-life was shortened in the Renal Disease group ( $113.4 \pm 11.3$  vs  $136.5 \pm 13.0 \text{ min}$ ;  $P < 0.05$ ). A mild reduction in blood pressure occurred in most volunteers. Although most volunteers were sedated by dexmedetomidine, renal disease volunteers were sedated for a longer period of time. **IMPLICATIONS:** The pharmacokinetics of dexmedetomidine in volunteers with severe renal impairment differed little from those in volunteers with normal renal function. In addition, there were no clinically significant differences in the hemodynamic responses to dexmedetomidine. However, dexmedetomidine resulted in more prolonged sedation in subjects with renal disease.

PMID: 11682398

Semin Respir Crit Care Med. 2001;22(2):165-74.

## Use of sedative medications in the intensive care unit.

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Current choices for sustained sedation in the critically ill include the benzodiazepines, the opiates, and propofol. Each of these groups of medications has their particular benefits: benzodiazepines provide the greatest amnesia, opiates are the only agents to provide analgesia, and propofol is the most easily titratable and the least likely to excessively accrue. The literature seems to favor propofol over the benzodiazepines as the most cost-effective solution to sustained sedation. A newly approved agent, dexmedetomidine, holds promise as a continuous infusion that can provide both anxiolysis and analgesia, but without the ventilatory depression seen in the other classes of sedatives. Further research is needed to determine the role of dexmedetomidine in the ICU. The emerging standard of care for sustained sedation is the use of standardized protocols, formulated with the help of clinical practice guidelines, and titrated with the guidance of sedation monitoring.

PMID: 16088671

[Chest](#). 2001 Dec;120(6 Suppl):445S-53S.

**[Trials comparing early vs late extubation following cardiovascular surgery.](#)** [Meade MO](#), [Guyatt G](#), [Butler R](#), [Elms B](#), [Hand L](#), [Ingram A](#), [Griffith L](#). Department of Medicine, McMaster University, Hamilton, Ontario, Canada.

We identified 10 randomized trials that compared alternative management approaches to patient care during and following cardiovascular surgery. One overall strategy involved a modification of anesthesia, in particular, a reduction in the dosage of fentanyl and benzodiazepine or the substitution of fentanyl for propofol (five randomized controlled trials [RCTs]). Pooled results show a shorter duration of ventilation (7 h) and a shorter duration of hospital stay (approximately 1 day) associated with lower anesthetic doses. The second strategy involved early vs late extubation once patients were admitted to the ICU (five RCTs). Pooled results show a shorter duration of ventilation (13 h) and a shorter duration of ICU stay (half a day) associated with early extubation. An additional 8 nonrandomized trials had findings that were consistent with the 10 RCTs. Reintubation, complications, and mortality rates were too low to draw conclusions about these outcomes. Overall, these studies indicate that anesthetic, sedation, and early-extubation strategies in selected cardiac surgery patients are associated with a shorter duration of mechanical ventilation and shorter lengths of ICU and hospital stays. PMID: 11742964

[J Cardiothorac Vasc Anesth](#). 1999 Apr;13(2):150-3.

**[Calcium chloride minimizes the hemodynamic effects of propofol in patients undergoing coronary artery bypass grafting.](#)**

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**OBJECTIVE:** To assess the hemodynamic effects of propofol and the counteracting effect of calcium chloride (CaCl<sub>2</sub>) in patients undergoing coronary artery bypass grafting (CABG). **DESIGN:** Prospective, randomized study. **SETTING:** University hospital, department of cardiac surgery. **PARTICIPANTS:** Fifty-eight patients undergoing elective CABG, divided into group A (n = 29) and group B (n = 29). **INTERVENTIONS:** Anesthesia was induced with a combination of fentanyl, 7 microg/kg; pancuronium, 0.1 mg/kg; and propofol, 1.5 mg/kg, administered over 60 seconds. A blinded investigator administered saline in group A patients and 10 mg/kg of CaCl<sub>2</sub> in group B patients at the same speed and same time as propofol administration through another lumen of the central venous catheter. **MEASUREMENTS AND MAIN RESULTS:** Hemodynamic data were obtained at baseline (T0), 2 minutes after anesthesia induction (T1), and 2 minutes after tracheal intubation (T2). Heart rate decreased significantly in group A patients (86.2±11.3 beats/min at T0 and 72.8±7.5 beats/min at T2; p < 0.001). Mean arterial pressure decreased significantly in patients in both groups (group A, 108.0±12.0 mmHg at T0; 74.6±14.6 mmHg at T2; p < 0.001 and group B, 106.0±10.2 mmHg at T0; 90.4±10.0 mmHg at T2; p < 0.05). Stroke volume index, cardiac index, and cardiac output decreased in group A patients (39.4±4.1 mL/beat/m<sup>2</sup> at T0 and 28.8±5.2 mL/beat/m<sup>2</sup> at T2; p < 0.05; 3.4±0.6 L/min/m<sup>2</sup> at T0 and 1.9±0.3 L/min/m<sup>2</sup> at T2; p < 0.001; 5.9±0.9 L/min at T0 and 3.4±0.4 L/min at T2; p < 0.001, respectively), whereas in group B patients, changes were negligible (38.1±7.0 mL/beat/m<sup>2</sup> at T0 v 35.7±6.6 mL/beat/m<sup>2</sup> at T2; (NS) 3.3±0.5 L/min/m<sup>2</sup> at T0 v 2.7±0.3 L/min/m<sup>2</sup> at T2; (NS) 5.7±0.9 L/min at T0 v 4.7±0.5 L/min at T2; (NS), respectively). **CONCLUSION:** Simultaneous administration of CaCl<sub>2</sub> during the induction of anesthesia minimizes the potential negative effect of propofol on cardiac function in cardiac patients.

Publication Types: [Clinical Trial](#) [Randomized Controlled Trial](#)

PMID: 10230947

**Table 1. Main Characteristics of Patients**

	Group A	Group B
Sex (M/F)	23/6	22/7
Age (yr)	60 ± 2.1	59 ± 8.8
Weight (kg)	67.2 ± 4.3	68.6 ± 3.2
BSA (m <sup>2</sup> )	1.73 ± 0.06	1.75 ± 0.02
Nitrates + Ca channel blockers (No. of patients)	22	20
Nitrates + β blockers (No. of patients)	7	9
Ca <sup>++</sup> (mmol/L) at T0	1.25 ± 0.12	1.20 ± 0.15
Ca <sup>++</sup> (mmol/L) at T2	1.14 ± 0.11	1.30 ± 0.09

NOTE. Group A patients received propofol, and group B patients received propofol plus CaCl<sub>2</sub>.

Abbreviation: BSA, body surface area.

**Table 2. Hemodynamic Data**

Group	Time					
	T0		T1		T2	
	A	B	A	B	A	B
HR (beats/min)	86.2 ± 11.3	84.8 ± 15.0	74.6 ± 12.4*	79.2 ± 8.3	72.8 ± 7.5*	75.6 ± 18.6
MAP (mmHg)	108.0 ± 12.0	106.0 ± 10.2	81.8 ± 7.7*	75.8 ± 6.9*	74.6 ± 14.6*	90.4 ± 10.0*
MPAP (mmHg)	22.0 ± 3.4	23.2 ± 4.5	19.8 ± 1.3	19.8 ± 4.6	20.0 ± 2.3	19.8 ± 2.7
PCWP (mmHg)	13.2 ± 3.1	13.8 ± 5.8	11.8 ± 1.9	12.2 ± 3.5	11.4 ± 1.8	11.6 ± 2.5
CVP (mmHg)	9.8 ± 1.5	10.0 ± 3.5	9.4 ± 1.1	10.4 ± 4.2	9.6 ± 1.1	10.4 ± 2.6
CO (L/min)	5.9 ± 0.9	5.7 ± 0.9	3.8 ± 0.4*	4.5 ± 0.3	3.4 ± 0.4*	4.7 ± 0.5
CI (L/min/m <sup>2</sup> )	3.4 ± 0.6	3.3 ± 0.5	2.2 ± 0.2*	2.6 ± 0.1	1.9 ± 0.3*	2.7 ± 0.3
SVI (mL/beat/m <sup>2</sup> )	39.4 ± 4.1	38.1 ± 7.0	29.6 ± 2.6*	32.8 ± 5.9	28.8 ± 5.2*	35.7 ± 6.6
SVRI (dyne · sec · cm <sup>-5</sup> /m <sup>2</sup> )	2,304 ± 247	2,327 ± 438	2,632 ± 240	2,167 ± 322	2,736 ± 568	2,462 ± 332
PVRI (dyne · sec · cm <sup>-5</sup> /m <sup>2</sup> )	216 ± 96	242 ± 110	294 ± 64*	257 ± 75	361 ± 84*	262 ± 97

NOTE. Values are expressed as mean ± standard deviation. Group A, propofol; group B, propofol + CaCl<sub>2</sub>.

Abbreviations: T0, baseline; T1, induction; T2, intubation; HR, heart rate; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; CVP, central venous pressure; CO, cardiac output; CI, cardiac index; SVI, stroke volume index; SVRI, systemic vascular resistances index; PVRI, pulmonary vascular resistances index.

\**p* < 0.05 from baseline data.

[Anesthesiology](#). 1997 Feb;86(2):331-45.

**Dexmedetomidine as an anesthetic adjunct in coronary artery bypass grafting.**

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**BACKGROUND:** Alpha 2-adrenergic agonists decrease sympathetic tone with ensuing attenuation of neuroendocrine and hemodynamic responses to anesthesia and surgery. The effects of dexmedetomidine, a highly specific alpha 2-adrenergic agonist, on these responses have not been reported in patients undergoing coronary artery bypass grafting. **METHODS:** Eighty patients scheduled for elective coronary artery bypass grafting received, in a double-blind manner, either a saline placebo or a dexmedetomidine infusion, initially 50 ng.kg-1.min-1 for 30 min before induction of anesthesia with fentanyl, and then 7 ng.kg-1.min-1 until the end of surgery. Filling pressures, blood pressure, and heart rate were controlled by intravenous fluid and by supplemental anesthetics and vasoactive drugs. **RESULTS:** Compared with placebo, dexmedetomidine decreased plasma norepinephrine concentrations by 90%, attenuated the increase of blood pressure during anesthesia (3 vs. 24 mmHg) and surgery (2 vs. 14 mmHg), but increased slightly the need for intravenous fluid challenge (29 vs. 20 patients) and induced more hypotension during cardiopulmonary bypass (9 vs. 0 patients). Dexmedetomidine decreased the incidence of intraoperative (2 vs. 13 patients) and postoperative (5 vs. 16 patients) tachycardia. Dexmedetomidine also decreased the need for additional doses of fentanyl (3.1 vs. 5.4), the increments of enflurane (4.4 vs. 5.6), the need for beta blockers (3 vs. 11 patients), and the incidence of fentanyl-induced muscle rigidity (15 vs. 33 patients) and postoperative shivering (13 vs. 23 patients). **CONCLUSIONS:** Intraoperative intravenous infusion of dexmedetomidine to patients undergoing coronary artery revascularization decreased intraoperative sympathetic tone and attenuated hyperdynamic responses to anesthesia and surgery but increased the propensity toward hypotension.

Publication Types: [Clinical Trial](#) , [Randomized Controlled Trial](#)

PMID: 9054252

[Anesthesiology](#). 1995 Mar;82(3):620-33.

## **Effects of perioperative dexmedetomidine infusion in patients undergoing vascular surgery.**

### **The Study of Perioperative Ischemia Research Group.**

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**BACKGROUND:** Dexmedetomidine, a highly selective alpha 2-adrenergic agonist, increases perioperative hemodynamic stability in healthy patients but decreases blood pressure and heart rate. The goal of this study was to evaluate, in a preliminary manner, the hemodynamic effects of perioperatively administered dexmedetomidine in surgical patients at high risk for coronary artery disease. **METHODS:** Twenty-four vascular surgery patients received a continuous infusion of placebo or one of three doses of dexmedetomidine, targeting plasma concentrations of 0.15 ng/ml (low dose), 0.30 ng/ml (medium dose), or 0.45 ng/ml (high dose) from 1 h before induction of anesthesia until 48 h postoperatively. All patients received standardized anesthesia and hemodynamic management. Blood pressure, heart rate, and Holter ECG were monitored; additional monitoring included continuous 12-lead ECG preoperatively, anesthetic concentrations and myocardial wall motion (echocardiography) intraoperatively, and cardiac enzymes postoperatively. **RESULTS:** Preoperatively, there was a decrease in heart rate (low dose 11%, medium dose 5%, high dose 20%) and systolic blood pressure (low dose 3%, medium dose 12%, high dose 20%) in patients receiving dexmedetomidine. Intraoperatively, dexmedetomidine groups required more vasoactive medications to maintain hemodynamics within predetermined limits. Postoperatively, dexmedetomidine groups had less tachycardia (minutes/monitored hours) than the placebo group (placebo 23 min/h; low dose 9 min/h, P = 0.006; medium dose 0.5 min/h, P = 0.004; high dose 2.3 min/h, P = 0.004). Bradycardia was rare in all groups. There were no myocardial infarctions or discernible trends in the laboratory results. **CONCLUSIONS:** Infusion of dexmedetomidine up to a targeted plasma concentration of 0.45 ng/ml appears to benefit perioperative hemodynamic management of surgical patients undergoing vascular surgery but required greater intraoperative pharmacologic intervention to support blood pressure and heart rate.

Publication Types: [Clinical Trial](#) , [Randomized Controlled Trial](#)

PMID: 7879930

[J Cardiothorac Vasc Anesth](#). 1995 Aug;9(4):368-72

## **Comparison of the use of a propofol infusion in cardiac surgical patients with normal and low cardiac output states.**

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**OBJECTIVES:** This study compared the hemodynamic effects of a propofol infusion with fentanyl analgesia in patients undergoing cardiac surgery with normal and low cardiac output states. Low cardiac output was defined as a cardiac index less than 2.5 L/min/m<sup>2</sup> with a minimum pulmonary capillary wedge pressure of 7 mmHg. **DESIGN:** A prospective and open study. **SETTING:** A single center cardiothoracic unit within a teaching hospital. **PARTICIPANTS:** Patients were assigned to group P, poor cardiac output or group N, normal cardiac output, after thermodilution pulmonary artery catheter assessments. **INTERVENTIONS:** Both groups received a propofol infusion, 8 mg/kg/hr, until induction of anesthesia, followed by 4 mg/kg/hr until the intensive care unit. Fentanyl, 15 micrograms/kg, and pancuronium, 0.15 mg/kg, were administered after induction. The lungs were ventilated with oxygen. **MEASUREMENTS AND MAIN RESULTS:** Hemodynamic assessments were repeated at intervals until cardiopulmonary bypass.

Changes within and between groups were compared using t tests on percentage change from baseline. Group Normal had significantly greater decreases in cardiac index, stroke volume, and left ventricular stroke work index than group Poor. There were comparable decreases in mean arterial pressure on induction of anesthesia, 14% and 8% in group Normal and group Poor, respectively. In both groups, right ventricular ejection fraction was unchanged. CONCLUSIONS: The use of a propofol infusion for induction and maintenance of anesthesia in patients with low cardiac output states undergoing cardiac surgery is not associated with clinically important myocardial depression nor is it contraindicated.

Publication Types: [Clinical Trial](#)

PMID: 7579104

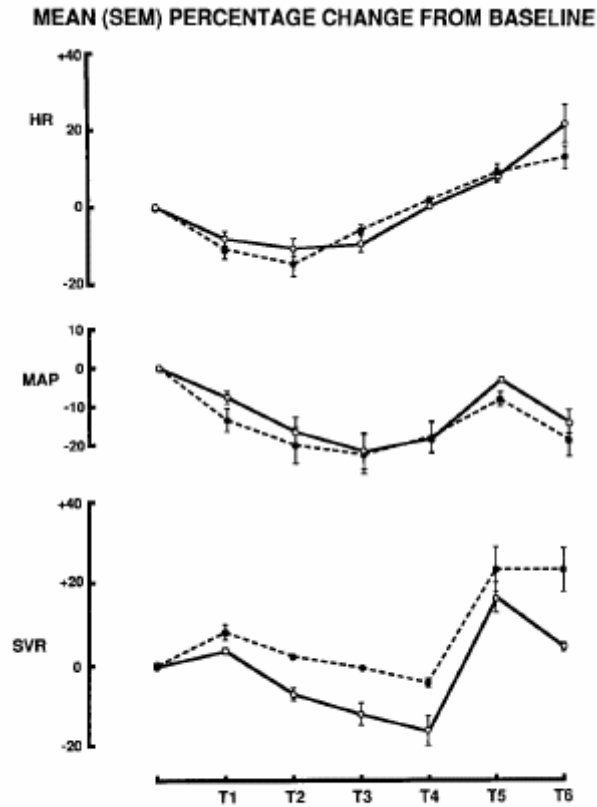


Fig 1 A comparison of HR, MAP, and SVR with the use of a propofol infusion in cardiac surgical patients with normal and poor cardiac outputs Group P, ○—○; group N, ●---●; \* $p < 0.001$  between groups.

MEAN (SEM) PERCENTAGE CHANGE FROM BASELINE

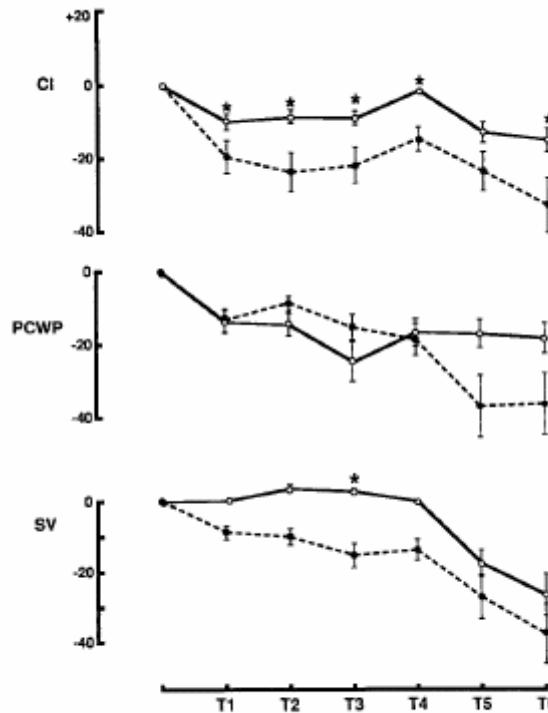


Fig 2. A comparison of CI, PCWP, and SV with the use of propofol in cardiac surgical patients with normal and poor cardiac outputs. Group P, ○—○, group N, ●---●; \**p* < 0.001 between groups.

[Anesthesiology](#). 1992 Dec;77(6):1134-42.

## Effects of intravenous dexmedetomidine in humans. II. Hemodynamic changes.

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Dexmedetomidine (DMED) is a novel clonidine-like compound known to have sedative, analgesic, and cardiovascular stabilizing qualities. DMED is a more highly selective alpha 2-adrenergic agonist than clonidine. This investigation examined the hemodynamic effects of four selected iv doses in consenting healthy male volunteers. In a randomized, double-blind, placebo-controlled trial subjects received 0 (n = 9), 0.25 (n = 6), 0.5 (n = 6), 1.0 (n = 6), or 2.0 (n = 10) micrograms/kg of DMED by infusion (2 min). ECG, heart rate (HR), arterial blood pressure (MABP), bioimpedance cardiac output (CO), and plasma catecholamines concentrations (CA) were monitored from 90 min before to 360 min after infusion. Plasma DMED concentrations were measured. DMED produced a maximum decrease in MABP at 60 min of 14%, 16%, 23%, and 27% for the 0.25, 0.5, 1.0, and 2.0 micrograms/kg groups, respectively (P < .05). At 330 min MABP remained below baseline by 8% and 17% at the two largest doses (P < .05). Both HR and CO decreased maximally by both 17% at 105 min. The two largest doses produced a transient (peak at 3 min lasting < 11 min) increase in MABP (16 +/- 2.5 and 24 +/- 10 mmHg, respectively; P < .05) with a concomitantly reduced CO (41%, 2 micrograms/kg; P < .05) and HR (22%, 2 micrograms/kg; P < .05), whereas systemic vascular resistance doubled. Even the lowest dose decreased CA immediately to values close to 20 pg/ml for 5 h. A 2-min iv infusion of DMED produced a transient increase in MABP and a longer lasting decrease in MABP and CA. These DMED doses were well tolerated in the healthy volunteers.

Publication Types: [Clinical Trial](#), [Randomized Controlled Trial](#)

PMID: 1361311

[Anesthesiology](#). 1992 Dec;77(6):1125-33

## Effects of intravenous dexmedetomidine in humans. I. Sedation, ventilation, and metabolic rate.

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Dexmedetomidine (DMED) is a highly selective centrally acting alpha 2-adrenergic agonist thought to provide significant sedation

without appreciable ventilatory effects. This double-blind, placebo-controlled experiment evaluated four dose levels of DMED (0.25, 0.5, 1.0, and 2.0 micrograms/kg intravenously over 2 min) in 37 healthy male volunteers. Measurements of sedation, arterial blood gases, resting ventilation, hypercapnic ventilatory response (HVR), and metabolic rate (O<sub>2</sub> consumption and CO<sub>2</sub> production) were performed at baseline, 10 min after DMED infusion, and thereafter at the end of each subsequent 45-min period. DMED caused sedation resulting in loss of responsiveness in most of the subjects administered 1.0 and 2.0 micrograms/kg; sedation was evident for 195 min following 2.0 micrograms/kg ( $P < .05$ ). Ten minutes following infusion of 1.0 and 2.0 micrograms/kg, PaCO<sub>2</sub> had increased by 5.0 and 4.2 mmHg, respectively ( $P < .05$ ), and 60 min following 2.0 micrograms/kg, VE had decreased by 28% ( $P < .05$ ). The placebo group showed a progressive increase in the HVR slope (50% increase by 330 min following the infusion;  $P < .05$ ). Overall, across all the DMED doses, the slope was decreased ( $P < .05$ ) at all times after DMED. The calculated ventilation at a PaCO<sub>2</sub> of 55 mmHg was decreased (39%;  $P < .05$ ) 10 min following 1.0 and 2.0 micrograms/kg, returning to control values by 285 min following 2.0 micrograms/kg. O<sub>2</sub> consumption increased 16% ( $P < .05$ ) at 10 min following 2.0 micrograms/kg; CO<sub>2</sub> production decreased (22% at 60 min). By 5 h postinfusion, both had returned to normal. (ABSTRACT TRUNCATED AT 250 WORDS)

Publication Types: [Clinical Trial](#), [Randomized Controlled Trial](#)

PMID: 1361310

[J Cardiothorac Vasc Anesth.](#) 1991 Jun;5(3):268-77.

## **Central analgesic mechanisms: a review of opioid receptor physiopharmacology and related antinociceptive systems.**

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Clinical applications of these principles, based on the increased understanding of central analgesic mechanisms, are already being undertaken. Not only does the use of intrathecal and epidural opioids have the potential to decrease pain and related morbidity after surgical procedures, but there is at least one study that demonstrates a significant reduction in both major morbidity and mortality in high-risk surgical patients in whom epidural anesthesia and analgesia were used. These principles are also useful for the management of patients undergoing cardiac surgery. Currently, high-dose narcotic anesthesia is the technique of choice for such patients because of the greater hemodynamic stability this anesthetic technique provides. However, breakthrough hypertension and tachycardia still occur, and prolonged postoperative ventilation is a necessary consequence due to the high doses of narcotics that are required. In one study of patients undergoing coronary artery surgery, preoperative administration of clonidine, 5 micrograms/kg, orally, was demonstrated to decrease fentanyl requirements by 45% (110 to 61 micrograms/kg) while producing a similar degree of hemodynamic stability as seen with high-dose fentanyl. Extubation times were not compared, but the significantly lower dosage of fentanyl in the clonidine-treated group would be expected to lead to an earlier extubation. Whether similar potentiation of narcotic effects would be seen with dexmedetomidine, which may also prevent narcotic-induced rigidity, has not been determined, but the clinical application of such synergistic and complementary agents is another consequence of the greater understanding of central analgesic mechanisms, and augurs well for the future.

Publication Types: [Review](#)

PMID: 1650613

[Anesth Analg.](#) 2006 Jul;103(1):52-6, table of contents

## **The use of dexmedetomidine in pediatric cardiac surgery.**

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We tested dexmedetomidine, an alpha<sub>2</sub> agonist, for its ability to decrease heart rate, arterial blood pressure, and neuroendocrinal responses during pediatric cardiac surgery. In a randomized, placebo-controlled study, 30 pediatric patients undergoing open heart surgery were randomly assigned to one of two equal groups. The control group received saline, whereas the treatment group (DEX group) received an initial bolus dose of dexmedetomidine (0.5 microg/kg) over 10 min, followed immediately by a continuous infusion of 0.5 microg.kg(-1).h(-1). Arterial blood pressure, heart rate, and sequential concentrations of circulating cortisol, epinephrine, norepinephrine, and blood glucose were measured. Relative to baseline, arterial blood pressure and heart rate decreased significantly after the administration of dexmedetomidine through skin incision. In the control group, patients' heart rate and arterial blood pressure measures increased after skin incision until the end of bypass ( $P < 0.05$ ). In both groups, plasma cortisol, epinephrine, norepinephrine, and blood glucose increased significantly relative to baseline, after sternotomy, and after bypass. However, the values were significantly higher in the control group compared with the DEX group ( $P < 0.05$ ). In conclusion, intraoperative dexmedetomidine infusion attenuated the hemodynamic and neuroendocrinal response to surgical trauma and cardiopulmonary bypass in pediatric patients undergoing corrective surgery for congenital heart disease.

Publication Types: [Randomized Controlled Trial](#)

## **Hemodynamic effects of dexmedetomidine in patients after cardiac surgery.**

[Ishikawa S](#), [Kugawa S](#), [Neya K](#), [Suzuki Y](#), [Kawasaki A](#), [Hayama T](#), [Ueda K](#).

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AIM: Dexmedetomidine hydrochloride (Prece-dex(R)) is a potent and highly selective central  $\alpha_2$ -adrenoreceptor agonist.

Dexmedetomidine has recently been approved as a new sedative drug, however, its hemodynamic effects on patients just after cardiac surgery has not been established. METHODS: Nineteen patients (14 males and 5 females) who underwent elective cardiovascular surgery were included in this study. The mean age of the patients was 65 years. Coronary artery bypass grafting was performed in 8 patients, aortic valve surgery in 5, mitral valve plus radiofrequency Maze surgery in 3, graft replacement of the ascending aorta in 2 and double valve replacement in 1. After surgery, dexmedetomidine was continuously infused for 3 h in total at a rate of 0.8 mg/kg/h for the initial 1 h and followed by 0.4 mg/kg/h. RESULTS: All patients were well sedated during dexmedetomidine infusion.

Dexmedetomidine infusion induced a decrease in systemic blood pressure and systemic vascular resistance index. Heart rate, stroke index, central venous pressure, pulmonary artery pressure and pulmonary artery resistance index remained unchanged. Mixed venous oxygen saturation significantly decreased and arterio-venous O<sub>2</sub> content difference increased after the beginning of dexmedetomidine infusion. CONCLUSIONS: Continuous dexmedetomidine infusion did not influence the hemodynamic condition except for the vasodilating effect, thus dexmedetomidine was considered to be a viable sedative drug after cardiac surgery.

PMID: 16858303

[Drugs R D](#). 2006;7(1):43-52.

## **Effect of dexmedetomidine on haemodynamic responses to laryngoscopy and intubation : perioperative haemodynamics and anaesthetic requirements.**

[Yildiz M](#), [Tavlan A](#), [Tuncer S](#), [Reisli R](#), [Yosunkaya A](#), [Otelcioglu S](#).

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BACKGROUND: Dexmedetomidine reduces the dose requirements for opioids and anaesthetic agents. The purpose of this study was to evaluate the effect of a single pre-induction intravenous dose of dexmedetomidine 1 microg/kg on cardiovascular response resulting from laryngoscopy and endotracheal intubation, need for anaesthetic agent and perioperative haemodynamic stability. METHODS: Fifty patients scheduled for elective minor surgery were randomised into two groups (dexmedetomidine group and placebo group, n = 25 in each group). During and after drug administration, the Ramsey sedation scale was applied every 5 minutes. Fentanyl 1 microg/kg was administered to all patients and thiopental was given until lash reflex disappeared. Anaesthesia continuation was maintained with 50% : 50%, oxygen : nitrous oxide. Sevoflurane concentration was adjusted to maintain systolic blood pressure within 20% of preoperative values. After extubation, the Steward awakening score was applied at 5 and 10 minutes. Haemodynamic parameters and adverse effects were recorded every 10 minutes for 1 hour after surgery. RESULTS: During intubation the need for thiopental and sevoflurane concentration were decreased by 39% and 92%, respectively, in the dexmedetomidine group compared with the placebo group. In all groups, blood pressure and heart rate increased after tracheal intubation; both were significantly lower in the dexmedetomidine group than in the placebo group ( $p < 0.05$ ). Fentanyl requirement during the operation was 74.20 +/- 10.53microg in the dexmedetomidine group and 84.00 +/- 27.04microg in the placebo group ( $p < 0.05$ ). At 5 minutes, the Steward scores were >6 in 56% of the dexmedetomidine group and in 4% of the placebo group ( $p < 0.05$ ). At 10 minutes, sedation scores were > or =4 in all patients in the dexmedetomidine group ( $p < 0.05$ ). Arterial blood pressure and heart rate in the postoperative period were significantly lower in the dexmedetomidine group compared with the placebo group ( $p < 0.05$ ). CONCLUSION: Preoperative administration of a single dose of dexmedetomidine resulted in progressive increases in sedation, blunted the haemodynamic responses during laryngoscopy, and reduced opioid and anaesthetic requirements. Furthermore, dexmedetomidine decreased blood pressure and heart rate as well as the recovery time after the operation.

Publication Types: [Randomized Controlled Trial](#)

PMID: 16620136

[J Cardiothorac Vasc Anesth](#). 2005 Oct;19(5):630-5.

## **A prospective, double-blind, randomized, placebo-controlled study of dexmedetomidine as an adjunct to epidural analgesia after thoracic surgery.**

[Wahlander S](#), [Frumento RJ](#), [Wagener G](#), [Saldana-Ferretti B](#), [Joshi RR](#), [Playford HR](#), [Sladen RN](#).

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OBJECTIVE: The purpose of this study was to test the hypothesis that after thoracic surgery, the supplementation of a low-dose thoracic epidural (ED) bupivacaine (0.125%) infusion by intravenous (IV) dexmedetomidine decreases analgesic requirement without causing respiratory depression. The primary endpoint was the need for additional ED bupivacaine administered through patient-controlled epidural analgesia (PCEA). Secondary endpoints included the requirement for supplemental opioids and the impact of

dexmedetomidine on CO<sub>2</sub> retention. DESIGN: A prospective, randomized, double-blinded study. SETTING: A major US tertiary care university hospital. PATIENTS: Twenty-eight patients scheduled to undergo elective thoracotomy for wedge resection, lobectomy, or pneumonectomy. INTERVENTIONS: On intensive care unit arrival, the thoracic ED catheter was loaded with 0.125% bupivacaine to a T4 sensory level and a continuous infusion of 0.125% bupivacaine without opioid was commenced at 4 mL/h. Patients were then randomized into 1 of 2 groups. The dexmedetomidine group received an IV loading dose of dexmedetomidine of 0.5 microg/kg over 20 minutes, followed by continuous IV infusion at 0.4 microg/kg/h. The placebo group received IV saline at the same calculated loading and infusion rates by volume. If necessary, supplemental analgesia (increased ED rate, ED fentanyl, ketorolac [IV]) was provided to ensure a visual analog scale (VAS) score of < or =3. MEASUREMENTS: The analgesic effect was monitored by the VAS, and the requirement for PCEA dosing and additional analgesics was recorded. Heart rate, blood pressure, and blood gases were also monitored. MAIN RESULTS: There was no significant difference in PCEA use and VAS score between the 2 groups, but requirement for supplemental ED fentanyl analgesia was significantly greater in the placebo group (66.1 +/- 95.6 v 5.3 +/- 17.1 microg, p = 0.039). Mean PaCO<sub>2</sub> was also significantly greater in the placebo group (40.3 +/- 4.1 v 43.9 +/- 4.3 mmHg, p = 0.04). Patients in the dexmedetomidine group exhibited significantly decreased heart rate (1 patient required and responded to atropine) and blood pressure (4 patients required and readily responded to IV fluid) compared with the placebo group. CONCLUSION: The authors conclude that in postthoracotomy patients, IV dexmedetomidine is a potentially effective analgesic adjunct to thoracic ED bupivacaine infusion and may decrease the requirement for opioids and potential for respiratory depression.

Publication Types: [Randomized Controlled Trial](#)

PMID: 16202898

Crit Care Nurs Clin North Am. 2005 Sep;17(3):211-23.

### **Tolerance and withdrawal issues with sedation.**

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The stay in an ICU is a complex mixture of providing optimal care while keeping the patient safe. Means of reducing the anxiety associated with the ICU stay include frequent reorientation and maintenance of patient comfort with sedation supplemented by analgesia as needed. The most common agents used to provide sedation include benzodiazepines, propofol, and the newer dexmedetomidine. Others include barbiturate agents, neuroleptics, clonidine, etomidate, ketamine, and supplemental opioid analgesics for pain control. A common complication of sedation is tolerance, which can lead to withdrawal if the sedation is discontinued hastily. This article evaluates the occurrence of tolerance and withdrawal in the most commonly used sedatives in critically ill patients.

PMID: 16115529

Crit Care. 2005 Jun;9(3):247-8. Epub 2005 Apr 18.

### **Narcotic-based sedation regimens for critically ill mechanically ventilated patients.**

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Sedatives and analgesics are routinely used in the intensive care unit to relieve pain and anxiety. These agents have numerous side effects and may contribute to poor outcomes such as increased length of mechanical ventilation, longer ICU stays and acute and long-term cognitive dysfunction. Modifying sedation paradigms utilizing either narcotic-based regimens with remifentanyl or fentanyl, or by using alpha<sub>2</sub> agonists such as dexmedetomidine may help in improving these outcomes in critically ill patients.

Publication Types: Comment

PMID: 15987412

Pharmacotherapy. 2005 May;25(5 Pt 2):8S-18S.

### **Adverse events associated with sedatives, analgesics, and other drugs that provide patient comfort in the intensive care unit.**

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Since the 2002 publication of multidisciplinary clinical practice guidelines for intensive care unit (ICU) sedation and analgesia, additional information regarding adverse drug events has been reported. Our understanding of the risks associated with these sedative and analgesic agents promises to improve outcomes by helping clinicians identify and respond to therapeutic misadventures sooner. This review focuses on many issues, including the potentially fatal consequences associated with the propofol infusion syndrome, the evolving understanding of propylene glycol intoxication associated with parenteral lorazepam, new data involving high-dose and long-

term dexmedetomidine therapy, haloperidol- and methadone-related prolongation of QTc intervals on the electrocardiogram, adverse events associated with atypical antipsychotics, and the potential for nonsteroidal antiinflammatory drugs to interfere with bone healing.

Publication Types: Review  
PMID: 15899744

J Intensive Care Med. 2005 Mar-Apr;20(2):118-23.

## **Dexmedetomidine in the treatment of withdrawal syndromes in cardiothoracic surgery patients.**

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Dexmedetomidine (Precedex, Abbott Laboratories, Abbott Park, IL) is an alpha 2 adrenergic agonist that possesses a high ratio of specificity for the alpha 2 versus the alpha 1 receptor. It is currently approved for the provision of sedation during mechanical ventilation in adults. Given previous experience with clonidine for the treatment of substance withdrawal and the preliminary anecdotal experience with dexmedetomidine, it appears that dexmedetomidine may be a useful agent for treatment of substance withdrawal in the intensive care setting. The authors present their experience with the use of dexmedetomidine to control withdrawal behavior in 3 patients following cardiothoracic surgery. Previous reports regarding the use of dexmedetomidine to treat withdrawal and its potential application in this clinical arena are reviewed.

Publication Types: Case Reports, Review  
PMID: 15855224

Intensive Care Med. 2004 Dec;30(12):2188-96. Epub 2004 Aug 26

## **Dexmedetomidine infusion for more than 24 hours in critically ill patients: sedative and cardiovascular effects.**

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**OBJECTIVE:** To assess the potential of dexmedetomidine for targeted sedation in complex Intensive Care (ICU) patients for >24 h. **DESIGN:** Prospective, open label, clinical trial. **SETTING:** Tertiary general ICU. **PATIENTS:** Twenty critically ill patients, mean APACHE II 23(+/-9). **INTERVENTIONS:** A continuous infusion of dexmedetomidine, median infusion time 71.5 (35-168) h, starting at 0.4 microg.kg.h without a loading dose and adjusted (0.2-0.7 microg.kg.h) to a target Ramsay Sedation Score (RSS) of 2-4. Rescue midazolam and/or morphine/fentanyl were given as clinically indicated. **MEASUREMENTS AND RESULTS:** Haemodynamic parameters and RSSs were collected until 24 h after cessation. An RSS 2-5 was achieved in 1,147 (83%) of observations with a reduction in RSS of 6 from 13% in the first 6 h to 3% between 18 h and 24 h. Sixteen patients needed minimal or no additional midazolam, median 4 mg/day (0.5-10) and ten required minimal or no additional analgesia, median 2 mg/day (0.5-4.5), 55 microg/day (14-63) of morphine/fentanyl. **RESULTS:** A 16% reduction in mean systolic blood pressure (SBP) and 21% reduction in heart rate (HR) occurred over the first 4 h followed by minimal (+/- 10%) changes throughout the infusion. A rise in SBP was observed in two patients. After abrupt cessation, SBP and HR monitored for 24 h rose by 7% and 11%, respectively. **CONCLUSIONS:** Dexmedetomidine was an effective sedative and analgesic sparing drug in critically ill patients when used without a loading dose for longer than 24 h with predictable falls in blood pressure and HR. There was no evidence of cardiovascular rebound 24 h after abrupt cessation of infusion.

Publication Types: Clinical Trial  
PMID: 15338124

Anesthesiology. 2004 Nov;101(5):1059-61.

## **Dexmedetomidine and opioid interactions: defining the role of dexmedetomidine for intensive care unit sedation.**

[Maze M](#), [Angst MS](#).

Publication Types: Comment, Editorial  
PMID: 15505438

J Neurosurg Anesthesiol. 2004 Oct;16(4):320; author reply 320-1.

## **Dexmedetomidine as primary sedative in CEA patients.**

[Shetty G](#), [Hever EJ](#), [Connolly ES](#).

Publication Types: Comment, Letter  
PMID: 15557842

[Anesth Analg](#). 2002 Aug;95(2):316-8, table of contents.

## **Treatment of persistent tachycardia with dexmedetomidine during off-pump cardiac surgery.**

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IMPLICATIONS: After unsuccessful treatment of intraoperative tachycardia with esmolol during off-pump revascularization, heart rate was successfully reduced with a bolus and infusion of dexmedetomidine.

Publication Types: [Case Reports](#)

PMID: 12145042

[J Neurosurg Anesthesiol](#). 2004 Apr;16(2):126-35.

## **Dexmedetomidine for awake carotid endarterectomy: efficacy, hemodynamic profile, and side effects.**

[Bekker AY](#), [Basile J](#), [Gold M](#), [Riles T](#), [Adelman M](#), [Cuff G](#), [Mathew JP](#), [Goldberg JD](#).

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A randomized, double-masked, placebo-controlled study was designed to compare dexmedetomidine as a primary sedative agent with a commonly used drug combination in patients undergoing awake carotid endarterectomy (CEA). Sixty-six patients undergoing CEA (ASA II-IV) were randomly assigned to receive either dexmedetomidine (total dose of 97.5 +/- 54.7 mcg) or normal saline (control). Supplemental doses of midazolam, fentanyl, and/or propofol were administered as deemed necessary by the anesthesiologist. An observer blinded to the study drug assessed sedation level (Observer's Assessment of Alertness-Sedation [OAA/S] scale). The primary outcomes were defined as the number of patients with an OAA/S score of 4 intraoperatively and an OAA/S score of 5 postoperatively. The authors also compared cardiorespiratory parameters, intra- and postoperative side effects, and complications. Chi-square tests were used to analyze the primary endpoints. All secondary parameters were analyzed using the Wilcoxon rank sum test. Three patients in the dexmedetomidine group (10%) had an OAA/S score of 4 at all four time points assessed intraoperatively, while no patient in the control group had a score of 4 at all the time points considered. Thirteen patients in the dexmedetomidine group had a score of 4 at three or more time points (42%) compared with six patients (19%) in the control group. Four patients in the control group (13%) and one patient in the dexmedetomidine group (3%) did not achieve a score of 4 at any of the four critical intraoperative time points (chi for association = 9.9,  $P < 0.05$ ; chi for a trend = 8.6,  $P < 0.004$ , with the trend favoring dexmedetomidine). More patients in the control group required treatment with metoprolol (26% vs. 6%,  $P = 0.04$ ) and labetalol (48% vs/ 6%,  $P < 0.01$ ). Plasma levels of norepinephrine were significantly lower in the dexmedetomidine group during and after surgery compared with the control group. Six patients (19%) in the dexmedetomidine group required intra-arterial shunts, while only two patients (6%) required shunts in the control group ( $P = 0.16$ ). These data show that the use of dexmedetomidine in patients undergoing awake CEA resulted in fewer fluctuations from the desired sedation level. Patients receiving dexmedetomidine required less antihypertensive therapy compared with the midazolam/fentanyl/propofol combination. The effect of dexmedetomidine on cerebrovascular circulation in the study population needs further investigation.

Publication Types: [Clinical Trial](#), [Randomized Controlled Trial](#)

PMID: 15021281

*J Clin Anesth*. 2006 Sep;18(6):422-6.

## **Dexmedetomidine infusion is associated with enhanced renal function after thoracic surgery.**

[Frumento RJ](#), [Logginidou HG](#), [Wahlander S](#), [Wagener G](#), [Playford HR](#), [Sladen RN](#).

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STUDY OBJECTIVE: To test the hypothesis that dexmedetomidine, a selective alpha-2 agonist, enhances urine flow rate and perioperative renal function, a post hoc analysis was conducted on a recently completed study of dexmedetomidine used as an adjunct to epidural analgesia after thoracotomy. DESIGN: Post hoc analysis of a randomized, placebo-controlled, double-blind clinical trial. SETTING: Tertiary-care university medical center. PATIENTS: 28 patients undergoing elective thoracotomy. INTERVENTIONS: Patients were prospectively randomized to receive a supplemental 24-hour intravenous infusion of either dexmedetomidine (0.4 microg kg(-1) h(-1),  $n = 14$ ) or saline placebo (equivalent infusion rate,  $n = 14$ ). MEASUREMENTS: Available renal parameters including urine output, calculated creatinine clearance (cCl(Cr)), daily serum creatinine level (S(Cr)), and the fractional change in S(Cr) level ( $\Delta S(Cr)\%$ ,  $[\text{peak postoperative S(Cr)} - \text{baseline S(Cr)}] / \text{baseline S(Cr)} \times 100$ ) were recorded. MAIN RESULTS: Values are expressed as means +/- SD. There were no significant differences in baseline values between the groups. The dexmedetomidine group had significantly greater cumulative urine output at postoperative hour 4 (473 +/- 35 vs 290 +/- 122 mL,  $P = 0.001$ ) and 12 (1033 +/- 240 vs 822 +/- 234 mL,  $P = 0.02$ ), although only 14% of the group received diuretic agents, compared with 43% in the control group. The dexmedetomidine group had significantly better preserved perioperative renal function compared with the control group, as assessed by  $\Delta S(Cr)\%$  (0.04% decrease vs 21% increase,  $P = 0.0007$ ) and cCl(Cr) (75.3 +/- 13.2 vs 62.5 +/- 15.5 mL/min,  $P = 0.02$ ). CONCLUSION: Dexmedetomidine infusion administered as a supplement to epidural analgesia induced diuresis in postthoracotomy patients with normal preoperative renal function and undergoing fluid restriction. Although this finding

may represent simple reversal of a tubular antidiuresis, the lower DeltaS(Cr)% and preservation of cCl(Cr) suggest a beneficial effect on glomerular filtration compared with controls.

[Randomized Controlled Trial](#) PMID: 16980158

In animal models involving general anesthesia, dexmedetomidine increases urinary output while decreasing urine osmolality and increasing free water clearance, suggesting that it reverses a prerenal antidiuretic response [8]. However, in a large multicenter study of intensive care unit (ICU) sedation after coronary artery bypass graft surgery, dexmedetomidine increased diuresis and decreased the incidence of high serum creatinine (Serum cr) values [9], suggesting a possible benefit on glomerular filtration.

Our data show that patients who received dexmedetomidine as part of their analgesic regimen had significantly greater urine output for the first 24 hours after surgery. This occurred despite equivalent fluid administration and the fact that more patients in the placebo group were given diuretic therapy. A possible mechanism for this finding is that dexmedetomidine decreases the release and/or the antidiuretic effect of arginine vasopressin (AVP).

It is therefore conceivable that because dexmedetomidine attenuates stress-induced increases in circulating norepinephrine, it may maintain renal blood flow and glomerular filtration. Indeed, it is well established that the administration of  $\alpha$ -2 adrenergic agonists can inhibit the surgical stress response [15-17] and thereby protect the kidney against the detrimental effects of adrenergic-mediated vasoconstriction [18]. There also may be direct vascular effects in the kidney. Dexmedetomidine decreases the sympathetically mediated presynaptic release of norepinephrine in the kidney [19], which could promote renal arterial vasodilatation.

There are several limitations in this study. It is a retrospective analysis of a prospective study that has shown a relationship between dexmedetomidine infusion and enhanced renal function, but does not establish a cause and effect relationship.

**Table 2** Patient demographic data

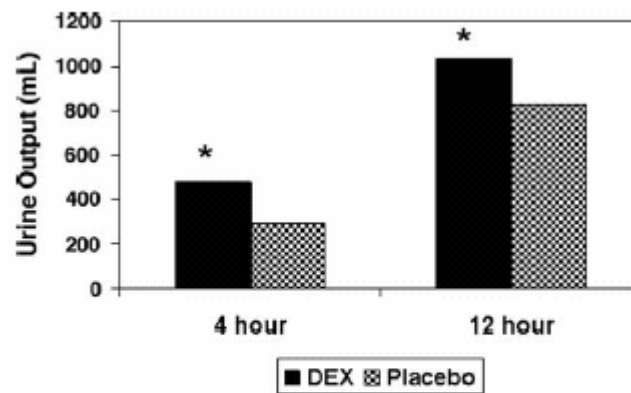
	Placebo group (n = 14)	Dexmedetomidine group (n = 14)
<b>Procedure</b>		
Lobectomy	12/14 (86%)	12/14 (86%)
Pneumonectomy	2/14 (14%)	2/14 (14%)
<b>Intraoperative data</b>		
Procedure length (min)	183 ± 36	191 ± 40
Crystalloid administered (mL)	712 ± 162	698 ± 113
EBL	169 ± 61	187 ± 62
Urine output (mL)	310 ± 42	290 ± 61
Fluid balance (mL)	+233 ± 89	+221 ± 99
<b>ICU (first 24 h)</b>		
Crystalloid administered (mL)	720 ± 92	679 ± 101
Fluid balance	-190 ± 77	-201 ± 88
Diuretic administered	6/14 (43%)	2/14 (14%)
NSAID administered	3/14 (21%)	2/14 (14%)

Data are means ± SD. No significant differences between groups were noted. EBL indicates estimated blood flow; NSAID, nonsteroidal anti-inflammatory drug.

**Table 1** Patient characteristics

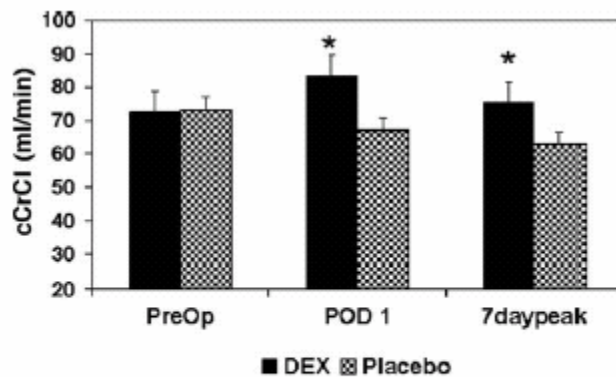
Characteristic	Placebo group (n = 14)	Dexmedetomidine group (n = 14)
Age (y)	65.7 ± 10.3	65.7 ± 9.0
Weight (kg)	69.8 ± 7.5	69.9 ± 6.3
Height (cm)	167.6 ± 8.6	168.9 ± 9.1
Gender (% men)	43	43
Race (% Caucasian)	86	79
Diabetes (%)	43	50
Hypertension (%)	57	64
COPD (%)	57	43

Data are means ± SD. No significant differences between groups were noted. COPD indicates chronic obstructive pulmonary disease.



\* $P < .05$

**Fig. 1** Urine output. POD1 indicates postoperative day 1; DEX, dexmedetomidine; \* $P < 0.05$ , compared with placebo for same time point.



\* $P < .05$

**Fig. 3** Change in calculated creatinine clearance ( $cCl_{Cr}$ ). \* $P < 0.05$ , compared with placebo for same time point.

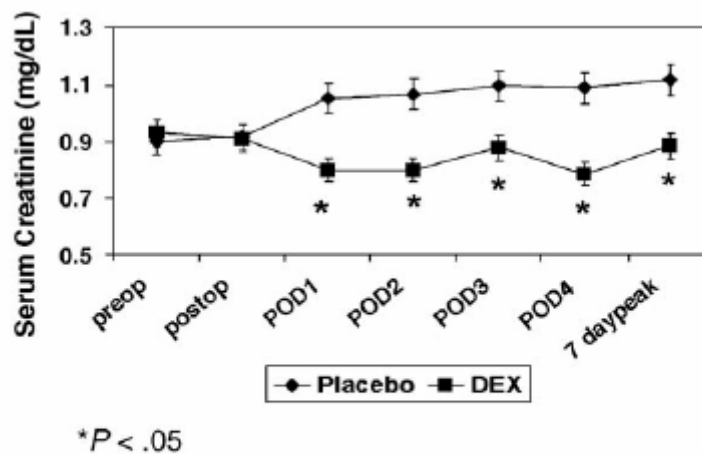


Fig. 2 Change in serum creatinine clearance over time. POD indicates postoperative day; \*P < 0.05, compared with placebo for same time point.

[Pharmacotherapy](#). 2005 Oct;25(10):1348-52.

## **Propofol-associated hypertriglyceridemia and pancreatitis in the intensive care unit: an analysis of frequency and risk factors.**

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**STUDY OBJECTIVES:** To characterize the frequency, severity, risk factors, and clinician response to propofol-associated hypertriglyceridemia and hypertriglyceridemia-associated pancreatitis. **DESIGN:** Retrospective analysis. **SETTING:** Medical and surgical intensive care units. **PATIENTS:** One hundred fifty-nine adult intensive care patients administered propofol for 24 hours or longer and who had at least one serum triglyceride concentration. **MEASUREMENTS AND MAIN RESULTS:** Patient records were reviewed to identify the frequency of hypertriglyceridemia (serum triglyceride concentration  $\geq$  400 mg/dl) and pancreatitis (amylase concentration  $\geq$  125 IU/L, lipase concentration  $\geq$  60 IU/L, and abdominal computed tomography scan or clinical examination findings consistent with pancreatitis). Of the 159 patients, 29 (18%) developed hypertriglyceridemia; six (21%) of the 29 had a serum triglyceride concentration of 1000 mg/dl or greater. The median maximum serum triglyceride concentration was 696 mg/dl (range 403-1737 mg/dl). At the time when hypertriglyceridemia was detected, the median infusion rate of propofol was 50 microg/kg/minute (range 5-110 microg/kg/min). The median time from the start of propofol therapy to identification of hypertriglyceridemia was 54 hours (range 14-319 hrs). Propofol was discontinued within 24 hours of detecting the hypertriglyceridemia 84% of the time. Compared with those who did not develop hypertriglyceridemia, patients who developed hypertriglyceridemia were older, had a longer intensive care unit stay, and received propofol for a longer duration; they were also more likely to be admitted to the medical versus the surgical intensive care unit. Pancreatitis developed in three (10%) of the 29 patients with hypertriglyceridemia. **CONCLUSION:** Hypertriglyceridemia and hypertriglyceridemia-associated pancreatitis are often seen in intensive care patients receiving propofol. Serum triglyceride concentrations should be routinely monitored in these patients. In addition, alternative sedation strategies should be considered when hypertriglyceridemia is detected.

PMID: 16185179 [PubMed - indexed for MEDLINE]

[Curr Opin Anaesthesiol](#). 2006 Aug;19(4):404-10.

## **Propofol infusion syndrome in anaesthesia and intensive care medicine.**

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**PURPOSE OF REVIEW:** Propofol infusion syndrome is a rare but often fatal syndrome, characterized by lactacidosis,

lipaemic plasma and cardiac failure, associated with propofol infusion over prolonged periods of time. As propofol is used worldwide, knowledge of propofol infusion syndrome is essential for all anaesthesiologists and intensive care physicians. This review will provide an update on reported cases, and describe recent findings relevant to the pathophysiology and clinical presentation of propofol infusion syndrome. **RECENT FINDINGS:** Case reports of propofol infusion syndrome have contributed new pathophysiological evidence. Reported cases of similar syndromes may represent initial propofol infusion syndrome, and may help to identify further risk factors such as low carbohydrate supply and early warning signs such as lactacidosis. Newly identified gene defects mimicking propofol infusion syndrome may elicit the underlying genetic susceptibility. Recommendations for the limitation of propofol use have been devised by various institutions. **SUMMARY:** Propofol infusion syndrome must be kept in mind as a rare but highly lethal complication of propofol use, not necessarily confined to the prolonged use of propofol. Dose limitations must be adhered to, and early warning signs such as lactacidosis should lead to the immediate cessation of propofol infusion.

Publication Types:

- [Review](#)

PMID: 16829722 [PubMed - indexed for MEDLINE]

[Intensive Care Med.](#) 2003 Sep;29(9):1417-25. Epub 2003 Aug 6.

Comment in:

## **The pathophysiology of propofol infusion syndrome: a simple name for a complex syndrome.**

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Propofol infusion syndrome (PRIS) is a rare and often fatal syndrome described in critically ill children undergoing long-term propofol infusion at high doses. Recently several cases have been reported in adults, too. The main features of the syndrome consist of cardiac failure, rhabdomyolysis, severe metabolic acidosis and renal failure. To date 21 paediatric cases and 14 adult cases have been described. These latter were mostly patients with acute neurological illnesses or acute inflammatory diseases complicated by severe infections or even sepsis, and receiving catecholamines and/or steroids in addition to propofol. Central nervous system activation with production of catecholamines and glucocorticoids, and systemic inflammation with cytokine production are priming factors for cardiac and peripheral muscle dysfunction. High-dose propofol, but also supportive treatments with catecholamines and corticosteroids, act as triggering factors. At the subcellular level, propofol impairs free fatty acid utilisation and mitochondrial activity. Imbalance between energy demand and utilisation is a key pathogenetic mechanism, which may lead to cardiac and peripheral muscle necrosis. Propofol infusion syndrome is multifactorial, and propofol, particularly when combined with catecholamines and/or steroids, acts as a triggering factor. The syndrome can be lethal and we suggest caution when using prolonged (>48 h) propofol sedation at doses higher than 5 mg/kg per h, particularly in patients with acute neurological or inflammatory illnesses. In these cases, alternative sedative agents should be considered. If unsuitable, strict monitoring of signs of myocytolysis is advisable.

Publication Types:

- [Review](#)

PMID: 12904852 [PubMed - indexed for MEDLINE]