Alpha2-agonists: the solution to better sedation or an expensive luxury?

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Conflicts of interest

- Received grants from:
  - GE Healthcare
  - Orion
  - BD Bioscience
- All managed through University of Edinburgh
- Chief Investigator: A2B trial (HTA funded)

Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit

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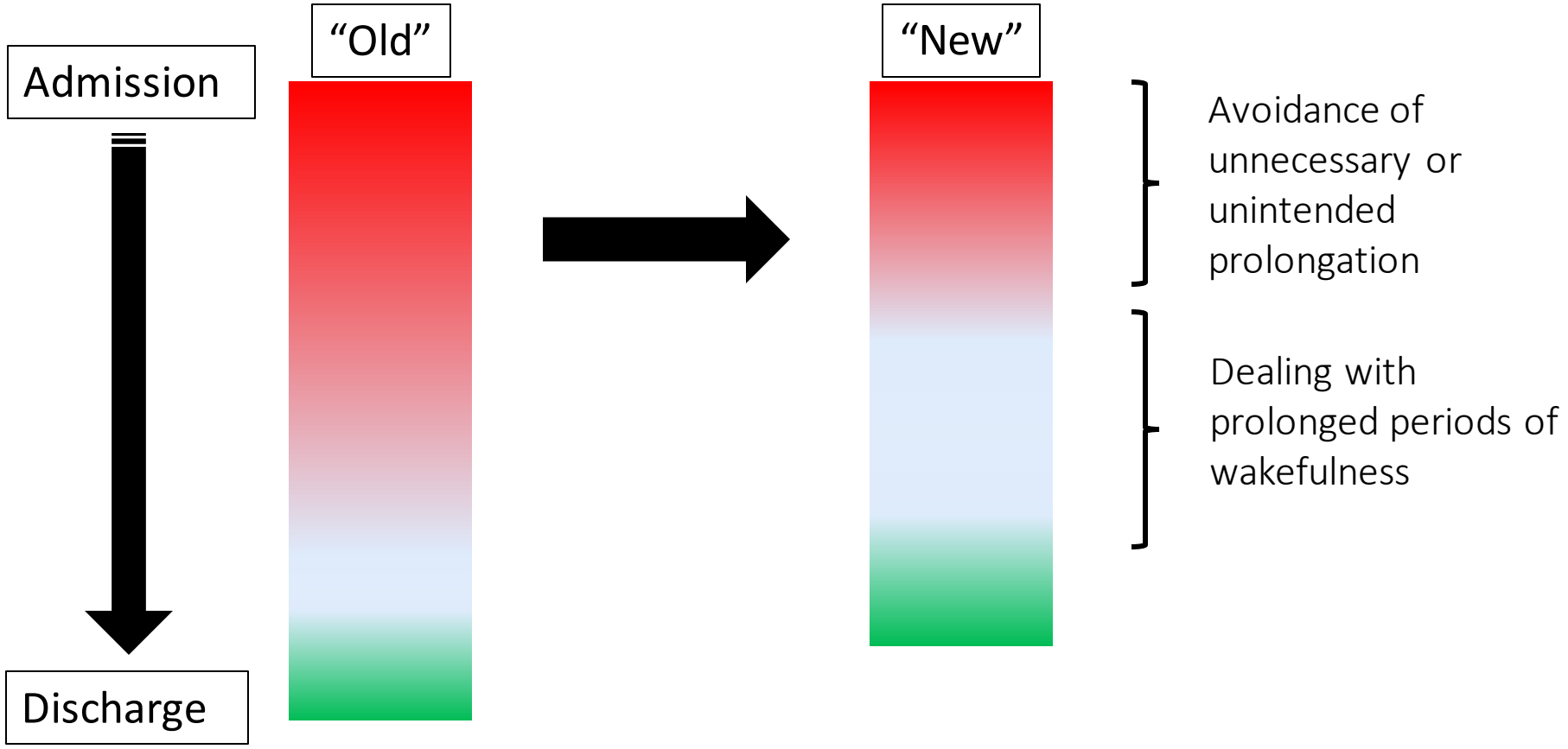
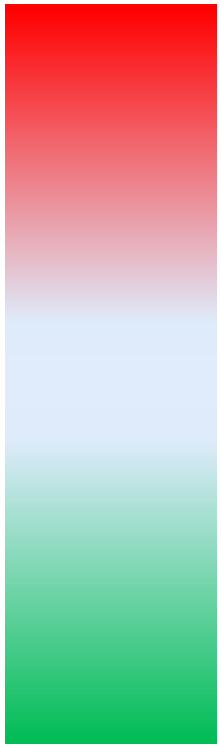
- Need for integrated approach
- Consider Pain, Agitation, and Delirium
- Avoid deep sedation
- Target ‘awake, comfortable, and communicative patients’ as early as possible

Implications of minimising sedation



Implications of minimising sedation



Tolerance of intubation and invasive ventilation
- Analgesia
- Antinociception
- Airway reflexes

Minimising risk of delirium

Managing agitation

Managing Pain/discomfort

Patient recall of intensive care

- Pain and frightening memories are frequently recalled by ICU survivors

  Chanques G et al. *Anesthesiology* 2007;107:858-60.

- Frightening and delusional memories associated with post-trauma psychological morbidity after critical illness

  Parker AM et al. *Critical Care Medicine* 2015; 43(5):1121-9

Outcome of delirium in critically ill patients: systematic review and meta-analysis

Jorge I F Salluh,[1] Han Wang,[2] Eric B Schneider,[2] Neeraja Nagaraja,[2] Gayane Yenokyan,[3] Abdulla Damluji,[4] Rodrigo B Serafim,[1,5] Robert D Stevens[6]

Cite this as: *BMJ* 2015;350:h2538
doi: 10.1136/bmj.h2538

42 studies

Delirium occurred (as dichotomous variable) in 32% of patients

Delirium associated with:

- Mortality during admission (risk ratio 2.19 (CI 1.78 to 2.70; P<0.001)
- Longer durations of mechanical ventilation, ICU stay, hospital stay
- Higher incidence of cognitive dysfunction among survivors

Aims

- Alpha2 agonist properties
- Clonidine versus dexmedetomidine
- Role in ICU sedation
- Role in perioperative practice
- The A2B trial

Alpha2 agonists

- Act primarily at brain stem locus coeruleus
- Dose-dependent decrease in activity of noradrenergic neurons in the brain stem via post-synaptic receptor-mediated inhibition
- Increases the activity of inhibitory gamma-aminobutyric acid (GABA) neurons
- Alter natural sleep pathways
- Additional analgesic properties via multiple sites, primarily at spinal cord level

Alpha2 agonists

Characteristics of alpha2 agonist sedation:

- Preserved muscle tone and ventilation
- Spontaneous and evoked movements
- Easy awakening by external stimuli
- Patients cooperative and can typically obey simple instructions

Other non-sedation actions

- Analgesia probably occurs via multiple sites, but primarily at the level of the spinal cord.
- Biphasic cardiovascular response (after bolus)
  - Initial hypertension (activation of receptors on peripheral vascular smooth muscle)
  - Centrally mediated sympathetic outflow inhibition and vagotonic actions. (hypotension and bradycardia)
- Minimal negative inotropic effects; may increase coronary blood flow
- Diuresis
- Dry mouth
- Decreased gut motility
- Possibly anti-inflammatory and immune modulating activity

Clonidine

- Introduced 1966 (treatment hypertension)
- Widely used for variety of disorders:
  - ADHD, tic disorders, drug withdrawal, restless leg syndrome
- Widespread off label use:
  - Stress and hyperarousal/anxiety syndromes
  - Pain medicine
  - ICU sedation
- Not licensed for ICU sedation or other ICU uses

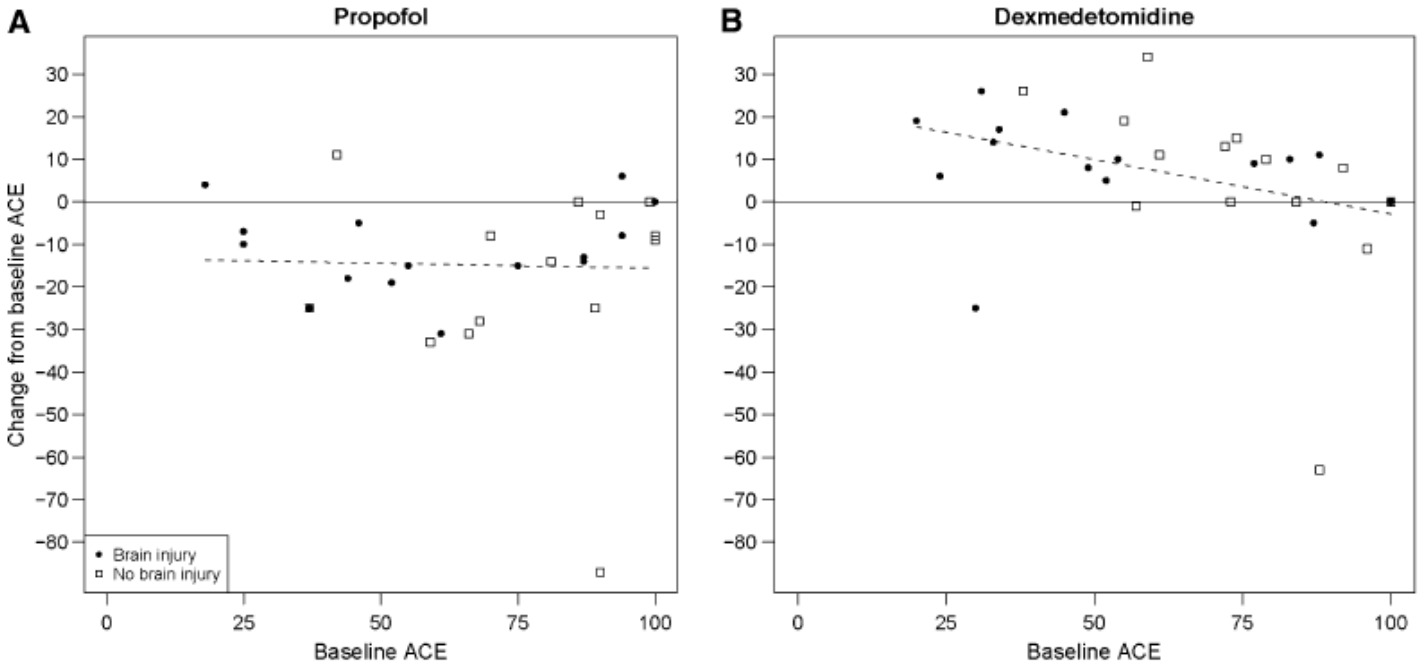
Dexmedetomidine

- Developed specifically for ICU sedation
- FDA license (initially in 1999) for ICU sedation and subsequently procedural sedation in non-intubated patients
- EU license (2011) for ICU sedation of intubated adult patients requiring light to moderate sedation (RASS score 0 to -3)

Cognitive improvement during continuous sedation in critically ill, awake and responsive patients: the Acute Neurological ICU Sedation Trial (ANIST)

Intensive Care Med (2010) 36:1505–1513

Cross over trial in patients with agitation: propofol vs dexmeditomidine
Primary outcome change on cognitive function



Sedative choice potentially important in assessing delirium

Aims

- Alpha2 agonist properties
- Clonidine versus dexmedetomidine
- Role in ICU sedation
- Role in perioperative practice
- The A2B trial

Dexmedetomidine versus Clonidine

Dexmedetomidine

- highly selective α2-agonist; α2:α1 receptor **selectivity ratio 1620:1**
- EU license since 2011
- >90% protein bound; unbound drug freely crosses blood–brain barrier.
- Highly metabolised by liver; inactive metabolites excreted by kidneys
- elimination half-life around 2 h (not prolonged by renal impairment)
- Estimated cost €100 per day

Clonidine

- lower α2-receptor selectivity; α2:α1 **selectivity ratio 220:1**
- Not licensed as ICU sedative
- less protein bound than dexmedetomidine (20-40%)
- hepatic metabolism to inactive metabolites, but around 65% excreted unchanged in the urine
- elimination half-life around 7 hours (range 6-23 hours)
- Prolonged in renal failure (18-41 hours)
- Estimated cost €8 per day

Aims

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Current UK sedation practice

- Propofol preferred sedative; alfentanil and fentanyl preferred opioid analgesics. 83% ICUs use agents in combination.
- Point prevalence study: 72% of patients receiving propofol; **8% clonidine**; **2% dexmedetomidine**
    - Critical care 2016;20(1):355

Survey Dec 2016 (159 responses from different UK ICUs; 70% response rate).

- 58% ICUs report using dexmedetomidine, but in less than 10% of patients.
- **90% ICUs report using clonidine**, in up to 25% of patients (administration route and protocols varied widely).
- <5% of ICUs had clear protocols defining indications or which agent to use first.

Current evidence relating to dexmedetomidine and clonidine for ICU sedation

Three recent SRs

- Cruickshank M, et al Alpha-2 agonists for sedation of mechanically ventilated adults in intensive care units: a systematic review. Health Technol Assess 2016;20(25):v-xx, 1-117.
  - 18 RCTs (2489 adult patients)
  - No high quality studies of clonidine (x1 small study comparing dexmedetomidine with clonidine)
  - 17 studies: dexmedetomidine with propofol or benzodiazepines
  - **No overall effect on mortality** RR 1.03 [95% confidence interval (CI) 0.85 to 1.24]
  - **Reduced length of ICU stay** (**mean difference -1.26 days**, 95% CI -1.96 to -0.55 days)
  - **Reduced time to extubation** (**mean difference -1.85 days**, 95% CI -2.61 to -1.09 days)
  - **No clear evidence for reduced delirium** (RR 0.83, 95% CI 0.65 to 1.06); high statistical heterogeneity.
- Cochrane review (2015;1:Cd010269)
  - Restricted to ICU patients requiring >24 hours MV
  - Very similar findings; mean reduction in MV duration 22% (95% CI 10% to 33%)
- Clonidine Review (Critical care 2017;21(1):75)
  - Low quality small trials; wide variability in population, dose, route, timing

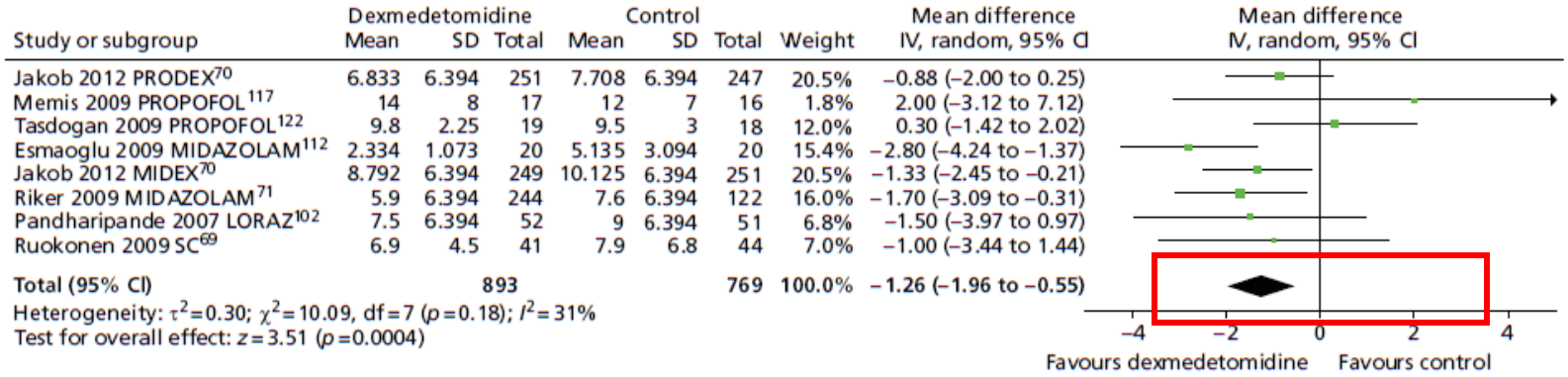


FIGURE 11 Meta-analysis for ICU length of stay: all available data (including transformed and imputed data). IV, inverse variance; LORAZ, lorazepam compared with dexmedetomidine; MIDAZOLAM, midazolam compared with dexmedetomidine; PROPOFOL, propofol compared with dexmedetomidine; SC, standard care compared with dexmedetomidine.

ICU length of stay

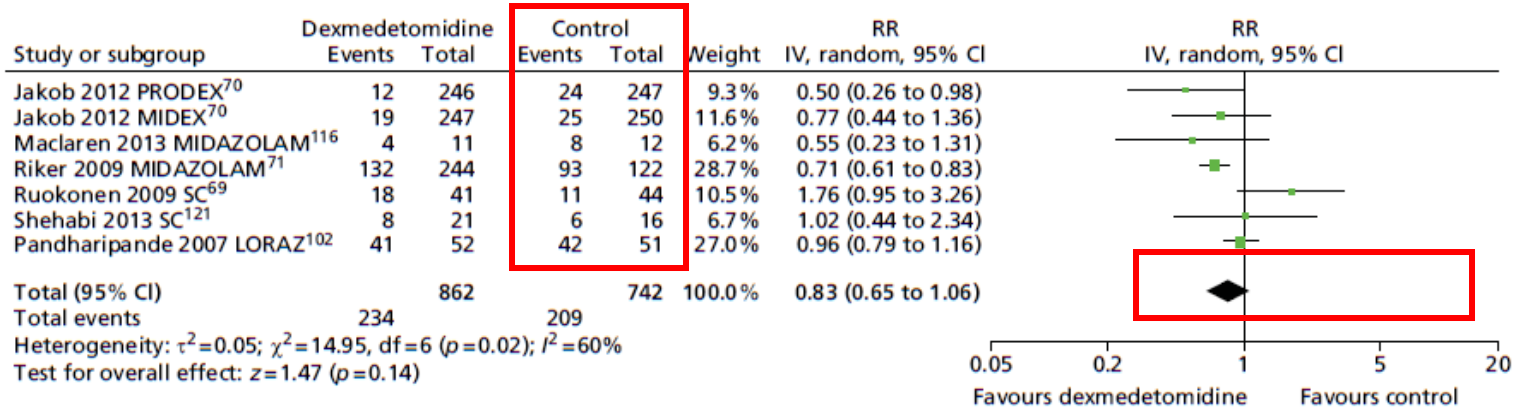


FIGURE 15 Meta-analysis for incidence of delirium. IV, inverse variance; LORAZ, lorazepam compared with dexmedetomidine; MIDAZOLAM, midazolam compared with dexmedetomidine; SC, standard care compared with dexmedetomidine.

Delirium

Clonidine for sedation in the critically ill: a systematic review and meta-analysis

Jing Gennie Wang[1], Emilie Belley-Coté[2], Lisa Burry[3,4], Mark Duffett[2,5], Timothy Karachi[1,6], Dan Perri[1,7], Waleed Alhazzani[1,2], Frederick D'Aragon[2], Hannah Wunsch[8,9,10] and Bram Rochwerg[1,2*]

Wang *et al. Critical Care* (2017) 21:75
DOI 10.1186/s13054-017-1610-8

- Outcomes: duration MV, mortality, delirium, use/duration sedatives, ICU/hospital length of stay
- Adverse effects: bradycardia, hypotension, withdrawal hypertension, unplanned extubation/line removal
- 8 RCTs (4 adult; 4 paediatric)
- 6 IV; 2 enteral
- Wide range of dose
- Most use as adjunct to other sedative
- Overall poor quality trials
- Adult trials size range 30 to 104 participants
- Paediatric trials size range 50 to 119 participants

Outcomes in systematic review and meta-analysis

- No difference in MV duration, length of stay outcomes or mortality
- No difference in sedative use
- Reduction in analgesic use
- Inadequate data to comment on delirium

Adverse events

- Increase in hypotension; no difference in bradycardia

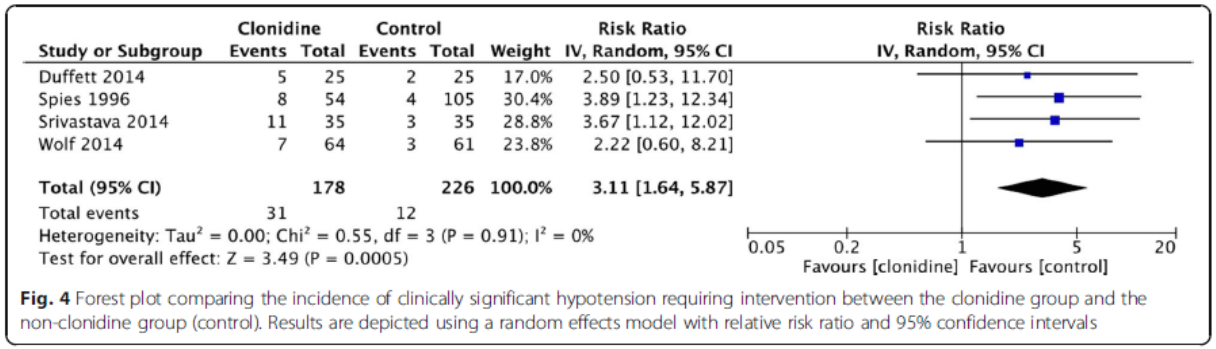


Fig. 4 Forest plot comparing the incidence of clinically significant hypotension requiring intervention between the clonidine group and the non-clonidine group (control). Results are depicted using a random effects model with relative risk ratio and 95% confidence intervals

Comparison of clonidine and dexmedetomidine for short term sedation of ICU patients

Srivastava et al. Indian J Crit Care Med 2014; 18:431-6

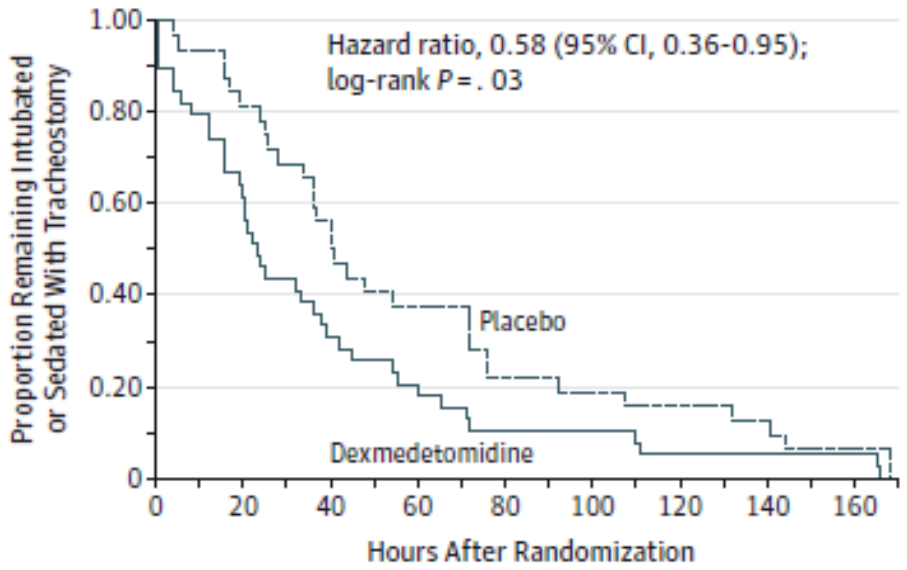
- MV adult patient; short mean duration (<1 day); 70 patients (35 per group)
- Direct comparison of dexmedetomidine versus clonidine as main agent
- More hypotension with clonidine
- Sedation quality better with dexmedetomidine

Effect of Dexmedetomidine Added to Standard Care on Ventilator-Free Time in Patients With Agitated Delirium

A Randomized Clinical Trial

07

Figure 2. Kaplan-Meier Analysis of the Proportion of Patients Remaining Intubated During the First 7 Days of the Study



No. at risk				
Dexmedetomidine	39	10	4	2
Placebo	32	13	6	2

Additional of dexmedetomidine to standard care associated with:

- Reduced time to extubation
- Quicker resolution of delirium
- Lower use of antipsychotics

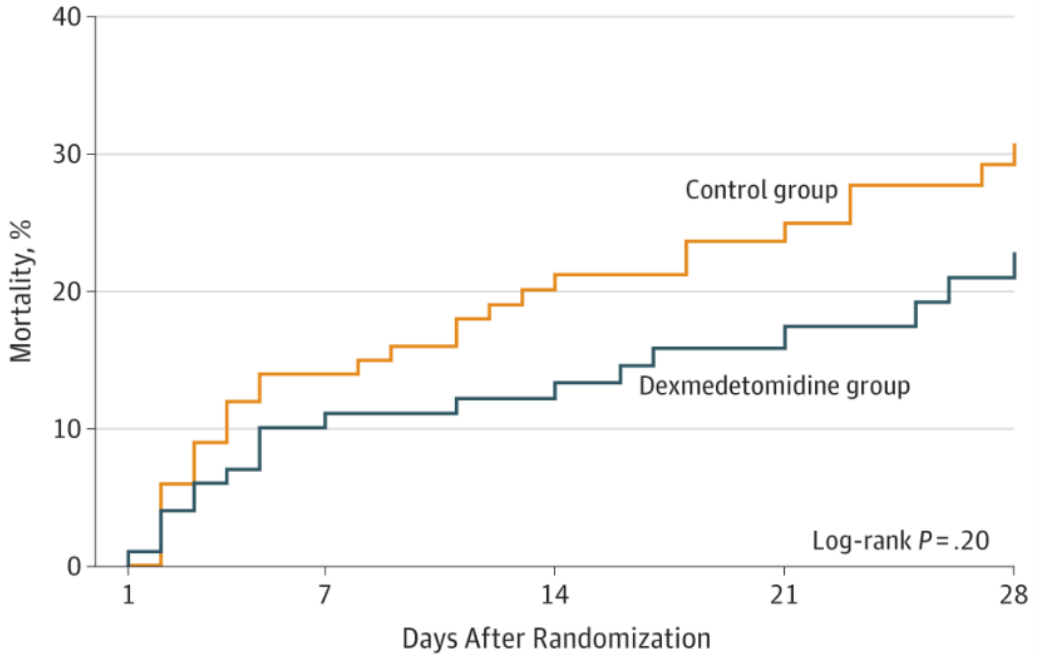
JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Dexmedetomidine on Mortality and Ventilator-Free Days in Patients Requiring Mechanical Ventilation With Sepsis

A Randomized Clinical Trial

Yu Kawazoe, MD, PhD; Kyohei Miyamoto, MD; Takeshi Morimoto, MD, PhD, MPH; Tomonori Yamamoto, MD; Akihiro Fuke, MD; Atsunori Hashimoto, MD, PhD; Hiroyuki Koami, MD; Satoru Beppu, MD, PhD; Yoichi Katayama, MD; Makoto Itoh, MD; Yoshinori Ohta, MD; Hitoshi Yamamura, MD, PhD; for the Dexmedetomidine for Sepsis in Intensive Care Unit Randomized Evaluation (DESIRE) Trial Investigators

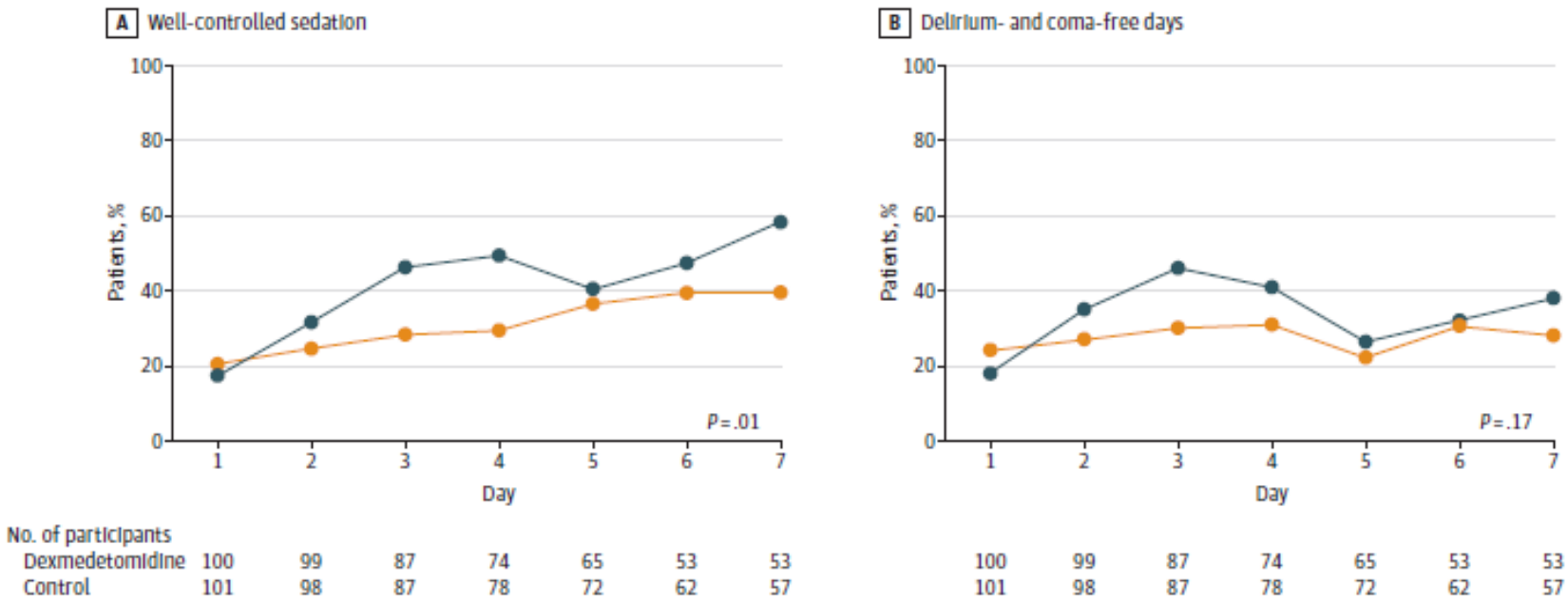
- Sepsis patients in Japan; mean APACHE 23
- Hypothesis based on post hoc analysis of MENDS trial
  - Septic sub-group mortality benefit (compared to lorazepam): 16% versus 41% mortality
  - Sample size for 20% ARR (200 patients)
- Unblinded trial; comparator usual care
- Co-primary outcome of 28 days mortality and ventilator free days
- Delirium as secondary outcome



No. at risk					
Dexmedetomidine	100	85	72	52	43
Control	101	86	70	55	46
Cumulative No. of events					
Dexmedetomidine	0	11	13	16	19
Control	0	14	21	24	28

Mortality 23% versus 31%; 8% ARR in mortality (ns)
VFDs 20 days versus 18 days (ns)

JAMA. Published online March 21, 2017. doi:10.1001/jama.2017.2088



Improved sedation quality (as defined in trial)
No difference in delirium/coma

THE EFFECT OF ALPHA-2 AGONISTS ON THE INFLAMMATORY RESPONSE IN CRITICAL ILLNESS: A SYSTEMATIC REVIEW OF ANIMAL AND HUMAN STUDIES

Charles A Flanders, Alistair S Rocke, Stuart A Edwardson, Kenneth J Baillie, Timothy S Walsh

- Eligible studies:
  - animal or human
  - dexmedetomidine or clonidine
  - Search terms dexmedetomidine/clonidine, sepsis and inflammation
  - Studies with a biological measure of inflammation as an outcome

Summary of main findings in animal studies

In animal studies of sepsis and inflammation, consistent signals of anti-inflammatory properties.

Uncertain relationship to outcomes

Animal Studies

Inflammatory Molecule	Alteration with alpha-2 agonist	Location
Myeloperoxidase	Decreased	Lung tissue Bronchoalveolar lavage fluid Epigastric skin tissue flap
Nuclear factor kappa B	Decreased	Lung tissue Bronchoalveolar lavage fluid Myocardial tissue
Nitric Oxide/inducible nitric oxide synthase mRNA	Decreased	Lung tissue Serum Epigastric skin tissue flap
Tumour Necrosis Factor-alpha	Decreased	Lung tissue Bronchoalveolar lavage fluid Serum Myocardial tissue
Interleukin-6	Decreased	Lung tissue Bronchoalveolar lavage fluid Serum Myocardial tissue
Toll-Like Receptor 4	Decreased	Lung tissue Intestinal tissue Myocardial tissue
Myeloid Differentiation Primary Response 88 (MyD88)	Decresaed	Lung tissue Myocardial tissue
Interleukin-10	Decreased	Serum
Vascular endothelial growth factor	Increased	Lung tissue
Vascular endothelial growth factor receptors 1 and 2	Increased	Lung tissue
Interleukin-1b	Decreased	Lung tissue Serum Myocardial tissue
Alpha-7 nicotinic acetylcholine receptor	Increased	Myocardial tissue
Organic hyperoxides and superoxide radicals	Decreased	Lung tissue Hepatic tissue Ileal tissue
High Mobility Group Box 1 (HMGB1)	Decreased	Lung tissue Renal tissue Myocardial tissue Serum
Kidney Injury Molecule 1(KIM1)	Decreased	Renal tissue
B-actin	Decreased	Serum
Cyclo-oxygenase 2 (COX-2)	Decreased	Serum
Prostaglandin E2 (PGE2)	Decreased	Serum
Macrophage inflammatory protein 2 (MIP2)	Decreased	Serum
Lactate	Decreased	Serum
Malondialdehyde (MDA)	Decreased	Renal tissue Epigastric skin tissue flap

Summary of Human studies

Author	Population
Gao 2015	RCT of 50 patients undergoing elective lobectomy and one lung ventilation
Kang 2013	RCT of 47 patients undergoing elective laparoscopic cholecystemomy for chronic cholecystitis.
Kawazoe 2017	Multi centre RCT of 201 ventilated ICU patients with a diagnosis of sepsis.
Memis 2007	RCT of 40 ventilated ICU patients with a diagnosis of bacterial sepsis.
Tasdogan 2009	RCT of 40 ventilated ICU patients. All patients were post-ileal surgery and had scored at least 2 sepsis criteria.
Ueki 2014	RCT of 37 patients undergoing elective cardiac surgery involving cardiopulmonary bypass.
Venn 2001	RCT of 20 ventilated ICU patients post-elective abdominopelvic surgery.
Yongsuk 2014	RCT of 46 patients undergoing elective laparoscopic cholecystectomy.
Zhou 2017	RCT of 40 patients undergoing elective multilevel spinal fusion operations.

All studies used dexmedetomidine
Variable dose (0.5-2.5 microgram/kg/hour)

Human Studies			
Inflammatory Molecule	**Alteration with alpha-2 agonist**	**Location**	**Number of studies**
Interferon Gamma	Increased (avoided decrease seen in placebo group)	Serum	1/1
Tumour Necrosis Factor-alpha	**Decreased**	**Serum**	**5/5**
Superoxide Dismutase (SOD)	Decreased	Serum	1/1
Malondialdehyde (MDA)	Decreased	Serum	1/1
Heme-oxygenase 1 (HO-1)	Decreased	Lung tissue	
White cell count	Decreased	Serum	2/2
Interleukin-1b	**Decreased**	**Serum**	**3/3**
Interleukin-6	**Decreased**	**Serum**	**4/6**
Interleukin-10	Decreased	Serum	1/1
C Reactive Protein (CRP)	**Decreased**	**Serum**	**4/4**
Procalcitonin	No statistically significant change	Serum	1/1
Prealbumin	No statistically significant change	Serum	1/1
Nuclear Factor Kappa B	Decreased	Serum	1/1
High Mobility Group Box 1 (HMGB1)	Decreased	Serum	1/1

Early Sedation with Dexmedetomidine in Critically Ill Patients

DOI: 10.1056/NEJMoa1904710

Y. Shehabi, B.D. Howe, R. Bellomo, Y.M. Arabi, M. Bailey, F.E. Bass, S. Bin Kadiman, C.J. McArthur, L. Murray, M.C. Reade, I.M. Seppelt, J. Takala, M.P. Wise, and S.A. Webb, for the ANZICS Clinical Trials Group and the SPICE III Investigators*

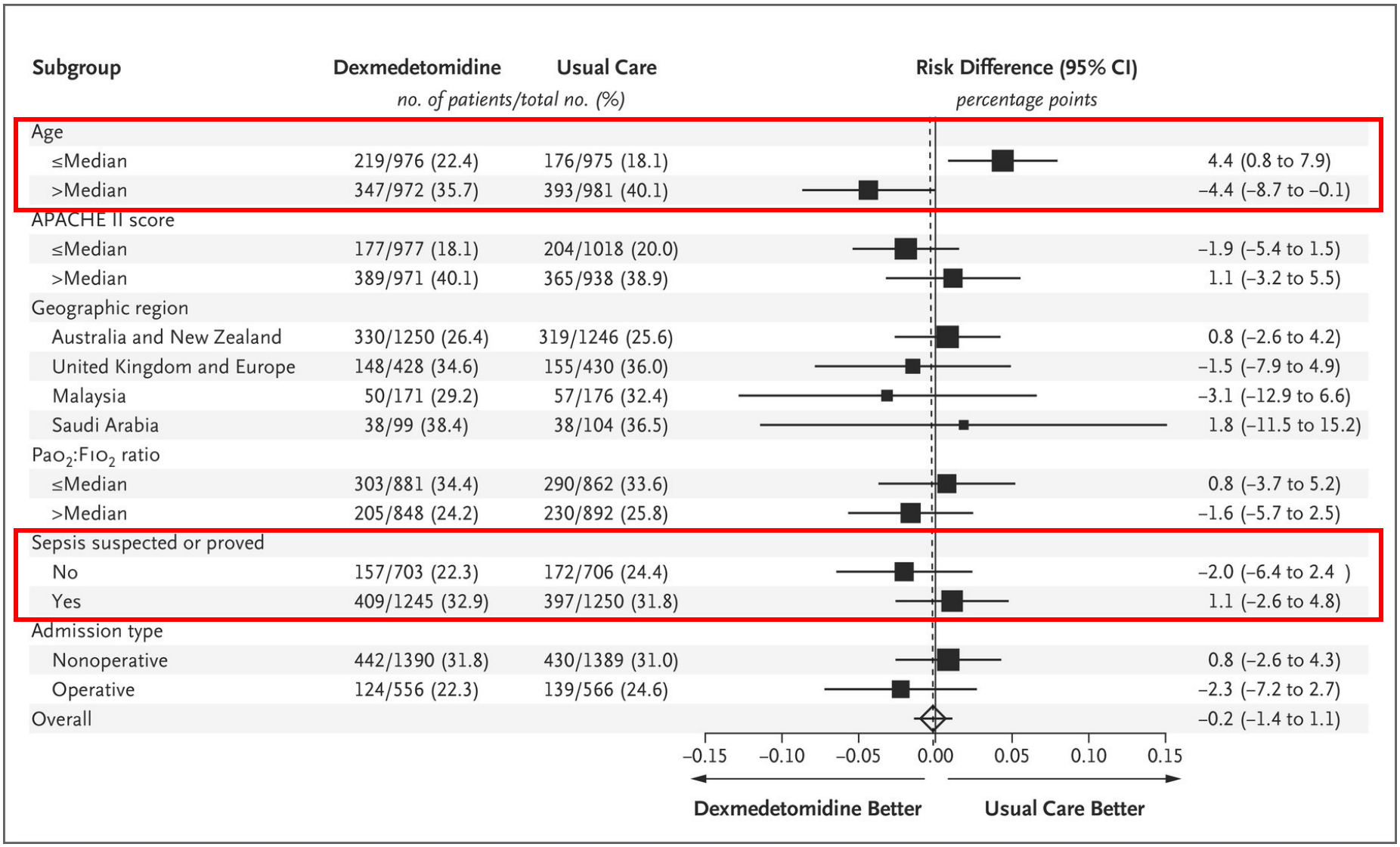
Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Dexmedetomidine (N=1954)	Usual Care (N=1964)
Age — yr	61.2±15.5	61.4±15.3
Male sex — no. %	1184 (60.6)	1231 (62.7)
Weight — kg	81.8±23.2	83.5±24.9
Score on APACHE II†	22.1±7.7	21.9±7.7
Suspected or proven sepsis — no. (%)	1248 (63.9)	1256 (64.0)
Median time from eligibility to randomization (IQR) — hr‡	4.7 (1.9 to 8.7)	4.4 (1.7 to 8.6)
Diabetes mellitus treated with insulin — no. (%)	185 (9.5)	205 (10.4)
Type of ICU admission — no. (%)		
Operative	536 (27.4)	550 (28.0)
Nonoperative	1417 (72.6)	1414 (72.0)
Admission diagnosis — no. (%)§		
Respiratory disorder	780 (39.9)	796 (40.5)
Sepsis¶	312 (16.0)	325 (16.5)
Gastrointestinal disorder	315 (16.1)	324 (16.5)
Cardiovascular disorder	300 (15.4)	279 (14.2)
Trauma	83 (4.2)	84 (4.3)
Neurologic disorder	26 (1.3)	24 (1.2)
Metabolic or endocrine disorder	26 (1.3)	21 (1.1)
Renal disorder	19 (1.0)	22 (1.1)
Hematologic disorder	12 (0.6)	9 (0.5)
Musculoskeletal or skin disorder	63 (3.2)	63 (3.2)
Other diagnosis	17 (0.9)	17 (0.9)
Median ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (IQR)‖	197 (136 to 293)	200 (133 to 284)
Median RASS score (IQR)**	−4 (−5 to −2)	−4 (−5 to −2)

Table 2. Clinical Outcomes.*

Outcome	Dexmedetomidine (N=1948)	Usual Care (N=1956)	Odds Ratio (95% CI)	Adjusted Risk Difference (95% CI)†
Death from any cause at 90 days: primary outcome — no. (%)	566 (29.1)	569 (29.1)	1.00 (0.87 to 1.15)	0.0 (–2.9 to 2.8)
Secondary outcomes				
Death at 180 days — no./total no. (%)	609/1935 (31.5)	610/1946 (31.3)	1.01 (0.88 to 1.16)	0.1 (–2.8 to 3.1)
Institutional dependency at 180 days — no./total no. (%)	89/1323 (6.7)	94/1337 (7.0)	0.96 (0.73 to 1.27)	–0.3 (–2.1 to 1.5)
Mean score on Short IQCODE at 180 days (95% CI)‡	3.14 (3.11 to 3.17)	3.08 (3.05 to 3.11)		0.06 (0.02 to 0.11)
Mean score on the EQ-5D-3L questionnaire (95% CI)§	69.8 (68.5 to 71.1)	70.2 (69.0 to 71.5)		–0.4 (–2.2 to 1.3)
Median no. of days free from coma or delirium (IQR)¶	24.0 (11.0 to 26.0)	23.0 (10.0 to 26.0)		1.0 (0.5 to 1.5)
Median no. of ventilator-free days (IQR)¶	23.0 (0.0 to 26.0)	22.0 (0.0 to 25.0)		1.0 (0.4 to 1.6)

- More serious adverse events in dexmedetomidine group (2.7% versus 0.4%)
- Almost all cardiovascular (bradycardia and hypotension)


Subgroup
Dexmedetomidine
Usual Care
no. of patients/total no. (%)
Risk Difference (95% CI)
percentage points
Age
≤Median 219/976 (22.4) 176/975 (18.1) 4.4 (0.8 to 7.9)
>Median 347/972 (35.7) 393/981 (40.1) −4.4 (−8.7 to −0.1)
APACHE II score
≤Median 177/977 (18.1) 204/1018 (20.0) −1.9 (−5.4 to 1.5)
>Median 389/971 (40.1) 365/938 (38.9) 1.1 (−3.2 to 5.5)
Geographic region
Australia and New Zealand 330/1250 (26.4) 319/1246 (25.6) 0.8 (−2.6 to 4.2)
United Kingdom and Europe 148/428 (34.6) 155/430 (36.0) −1.5 (−7.9 to 4.9)
Malaysia 50/171 (29.2) 57/176 (32.4) −3.1 (−12.9 to 6.6)
Saudi Arabia 38/99 (38.4) 38/104 (36.5) 1.8 (−11.5 to 15.2)
Pao2:Fio2 ratio
≤Median 303/881 (34.4) 290/862 (33.6) 0.8 (−3.7 to 5.2)
>Median 205/848 (24.2) 230/892 (25.8) −1.6 (−5.7 to 2.5)
Sepsis suspected or proved
No 157/703 (22.3) 172/706 (24.4) −2.0 (−6.4 to 2.4)
Yes 409/1245 (32.9) 397/1250 (31.8) 1.1 (−2.6 to 4.8)
Admission type
Nonoperative 442/1390 (31.8) 430/1389 (31.0) 0.8 (−2.6 to 4.3)
Operative 124/556 (22.3) 139/566 (24.6) −2.3 (−7.2 to 2.7)
Overall −0.2 (−1.4 to 1.1)
−0.15 −0.10 −0.05 0.00 0.05 0.10 0.15
Dexmedetomidine Better
Usual Care Better

Aims

- Alpha2 agonist properties
- Clonidine versus dexmedetomidine
- Role in ICU sedation
- Role in perioperative practice
- The A2B trial

Clonidine in patients undergoing noncardiac surgery.

Devereaux PJ, Sessler DI, Leslie K, et al. N Engl J Med. 2014;370:1504-13.

- POISE-2 trial 10,000 patients
- Hypothesis that reducing sympathetic activation would protect against cardiac events
- 0.2mg per day pre-operatively to post-operative day 3
- No effect on death/MI
- More patients had hypotension (48% versus 37%)
- Increased non-fatal cardiac arrest with clonidine (0.3% versus 0.1%)

BJA

British Journal of Anaesthesia, 121 (2): 384–397 (2018)

doi: 10.1016/j.bja.2018.04.046
Advance Access Publication Date: 22 June 2018
Review Article

NEUROSCIENCE AND NEUROANAESTHESIA

Efficacy of perioperative dexmedetomidine on postoperative delirium: systematic review and meta-analysis with trial sequential analysis of randomised controlled trials

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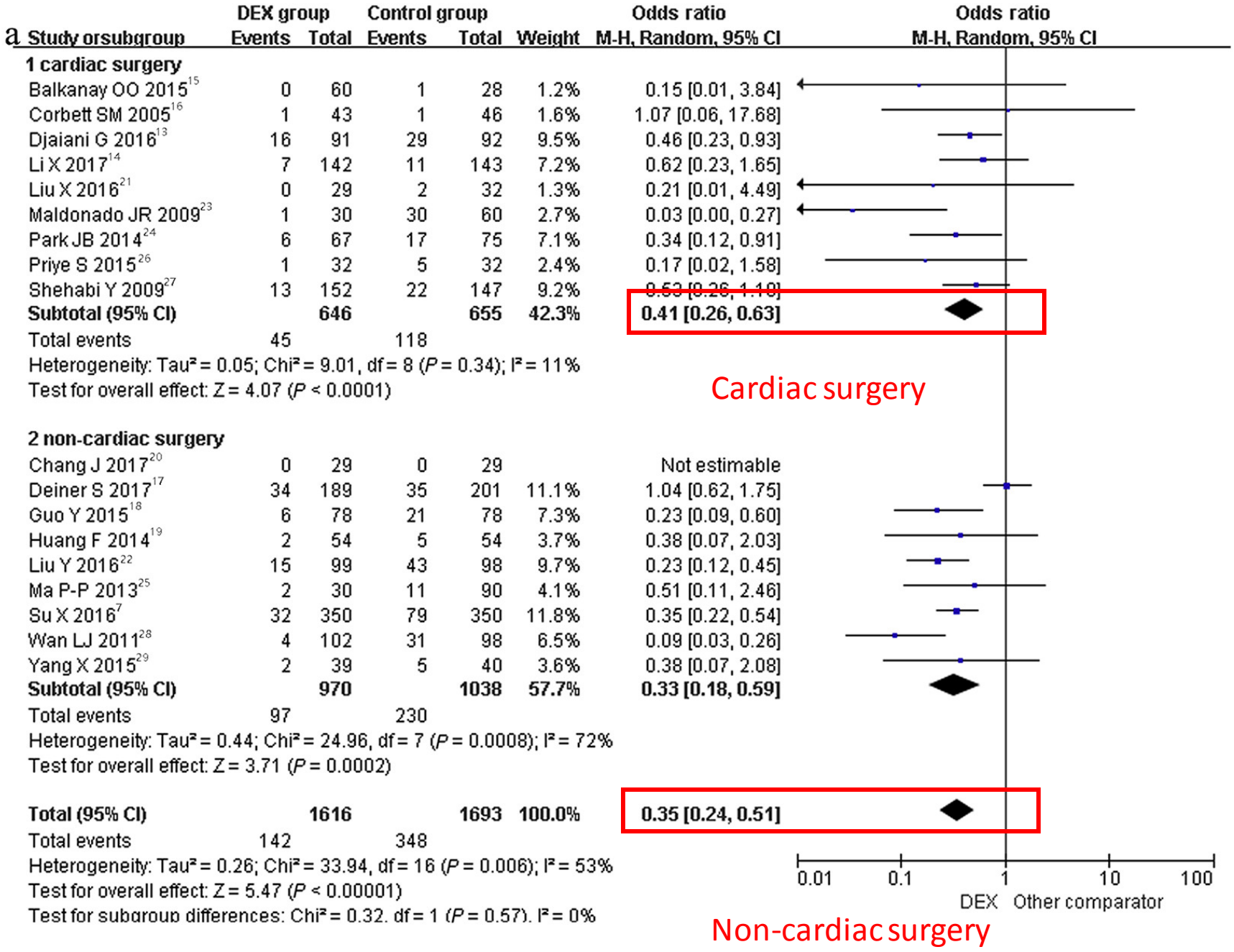
- 18 studies (3309 patients)
- Explored cardiac/non-cardiac; timing; age
- Typical dose 0.2microgram/kg/hour
- Variable duration and use of loading dose
- Explored range of secondary outcomes (mortality, length of stay)


a
Study orsubgroup
DEX group
Events
Total
Control group
Events
Total
Weight
Odds ratio
M-H, Random, 95% CI
Odds ratio
M-H, Random, 95% CI
1 cardiac surgery
Balkanay OO 2015[15] 0 60 1 28 1.2% 0.15 [0.01, 3.84]
Corbett SM 2005[16] 1 43 1 46 1.6% 1.07 [0.06, 17.68]
Djaiani G 2016[13] 16 91 29 92 9.5% 0.46 [0.23, 0.93]
Li X 2017[14] 7 142 11 143 7.2% 0.62 [0.23, 1.65]
Liu X 2016[21] 0 29 2 32 1.3% 0.21 [0.01, 4.49]
Maldonado JR 2009[23] 1 30 30 60 2.7% 0.03 [0.00, 0.27]
Park JB 2014[24] 6 67 17 75 7.1% 0.34 [0.12, 0.91]
Priye S 2015[26] 1 32 5 32 2.4% 0.17 [0.02, 1.58]
Shehabi Y 2009[27] 13 152 22 147 9.2% 0.53 [0.26, 1.10]
Subtotal (95% CI) 646 655 42.3% 0.41 [0.26, 0.63]
Total events 45 118
Heterogeneity: Tau² = 0.05; Chi² = 9.01, df = 8 (P = 0.34); I² = 11%
Test for overall effect: Z = 4.07 (P < 0.0001)
Cardiac surgery
2 non-cardiac surgery
Chang J 2017[20] 0 29 0 29 Not estimable
Deiner S 2017[17] 34 189 35 201 11.1% 1.04 [0.62, 1.75]
Guo Y 2015[18] 6 78 21 78 7.3% 0.23 [0.09, 0.60]
Huang F 2014[19] 2 54 5 54 3.7% 0.38 [0.07, 2.03]
Liu Y 2016[22] 15 99 43 98 9.7% 0.23 [0.12, 0.45]
Ma P-P 2013[25] 2 30 11 90 4.1% 0.51 [0.11, 2.46]
Su X 2016[7] 32 350 79 350 11.8% 0.35 [0.22, 0.54]
Wan LJ 2011[28] 4 102 31 98 6.5% 0.09 [0.03, 0.26]
Yang X 2015[29] 2 39 5 40 3.6% 0.38 [0.07, 2.08]
Subtotal (95% CI) 970 1038 57.7% 0.33 [0.18, 0.59]
Total events 97 230
Heterogeneity: Tau² = 0.44; Chi² = 24.96, df = 7 (P = 0.0008); I² = 72%
Test for overall effect: Z = 3.71 (P = 0.0002)
Total (95% CI) 1616 1693 100.0% 0.35 [0.24, 0.51]
Total events 142 348
Heterogeneity: Tau² = 0.26; Chi² = 33.94, df = 16 (P = 0.006); I² = 53%
Test for overall effect: Z = 5.47 (P < 0.00001)
Test for subgroup differences: Chi² = 0.32, df = 1 (P = 0.57), I² = 0%
0.01
0.1
1
10
100
DEX
Other comparator
Non-cardiac surgery

Peri/post operative dexmedetomidine

- Decreases post-operative delirium
- Consistent effects in all surgery types
- Effects seen in younger and older groups
- Suggestion of greater effect with longer infusions (around 10-12 hours or until end of MV)

- Inadequate information quality for mortality and length of stay outcomes
- Uncertainty about optimum dose/timing

Aims

- Alpha2 agonist properties
- Clonidine versus dexmedetomidine
- Role in ICU sedation
- Role in perioperative practice
- The A2B trial

ALPHA-2 AGONISTS FOR SEDATION TO PRODUCE BETTER OUTCOMES FROM CRITICAL ILLNESS

A randomised, parallel-group, allocation concealed, controlled, open, phase 3 pragmatic clinical and cost-effectiveness trial with internal pilot (HTA 16/93/01)

Aims

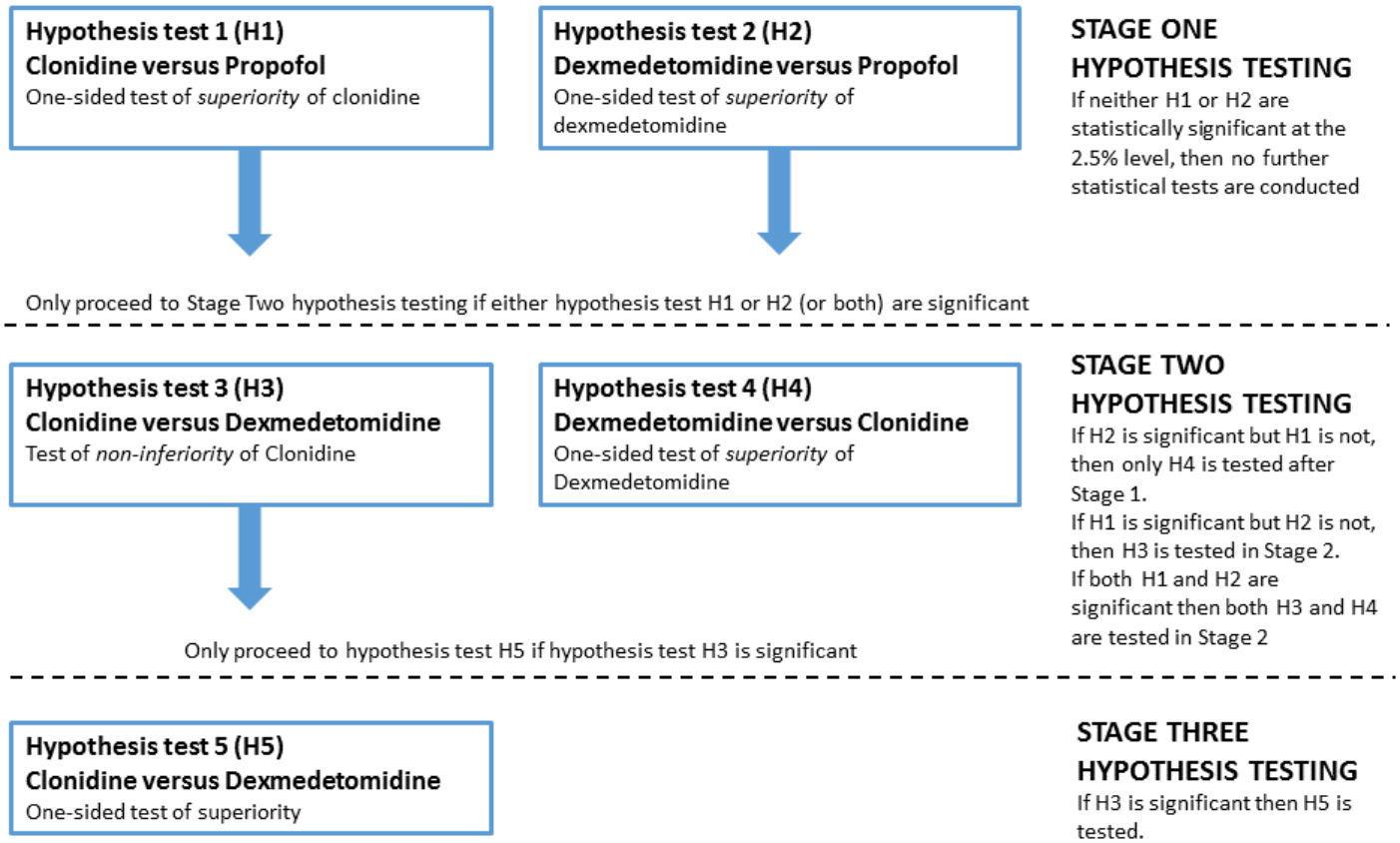
Overall aim

- To determine whether the α2-agonists clonidine or dexmedetomidine (or both) are clinically and cost-effective in MV ICU patients compared to current usual care.
- To determine which agent is most clinically effective and offers best value to the NHS given important differences in properties and cost between the drugs.

Trial

- 3 arms: dexmedetomidine *versus* clonidine *versus* usual care (propofol)
- Around 50 ICUs across the UK
- Target 1737 patients
- 8 sites open; 32 patients included

Analytic framework (hierarchical approach; serial gatekeeping to preserve power)



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