Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial

Xian Su, Zhao-Ting Meng, Xin-Hai Wu, Fan Cui, Hong-Liang Li, Dong-Xin Wang, Xi Zhu, Sai-Nan Zhu, Mervyn Maze, Daqing Ma

Summary

Background **Delirium is a postoperative complication that occurs frequently in patients older than 65 years, and presages adverse outcomes. We investigated whether prophylactic low-dose dexmedetomidine, a highly selective α_2 adrenoceptor agonist, could safely decrease the incidence of delirium in elderly patients after non-cardiac surgery.**

Methods **We did this randomised, double-blind, placebo-controlled trial in two tertiary-care hospitals in Beijing, China. We enrolled patients aged 65 years or older, who were admitted to intensive care units after non-cardiac surgery, with informed consent. We used a computer-generated randomisation sequence (in a 1:1 ratio) to randomly assign patients to receive either intravenous dexmedetomidine (0·1 μg/kg per h, from intensive care unit admission on the day of surgery until 0800 h on postoperative day 1), or placebo (intravenous normal saline). Participants, care providers, and investigators were all masked to group assignment. The primary endpoint was the incidence of delirium, assessed twice daily with the Confusion Assessment Method for intensive care units during the first 7 postoperative days. Analyses were done by intention-to-treat and safety populations. This study is registered with Chinese Clinical Trial Registry, www.chictr.org.cn, number ChiCTR-TRC-10000802.**

Findings **Between Aug 17, 2011, and Nov 20, 2013, of 2016 patients assessed, 700 were randomly assigned to receive either placebo (n=350) or dexmedetomidine (n=350). The incidence of postoperative delirium was significantly lower in the dexmedetomidine group (32 [9%] of 350 patients) than in the placebo group (79 [23%] of 350 patients; odds ratio [OR] 0·35, 95% CI 0·22–0·54; p<0·0001). Regarding safety, the incidence of hypertension was higher with placebo (62 [18%] of 350 patients) than with dexmedetomidine (34 [10%] of 350 patients; 0·50, 0·32–0·78; p=0·002). Tachycardia was also higher in patients given placebo (48 [14%] of 350 patients) than in patients given dexmedetomidine (23 [7%] of 350 patients; 0·44, 0·26–0·75; p=0·002). Occurrence of hypotension and bradycardia did not differ between groups.**

Interpretation **For patients aged over 65 years who are admitted to the intensive care unit after non-cardiac surgery, prophylactic low-dose dexmedetomidine significantly decreases the occurrence of delirium during the first 7 days after surgery. The therapy is safe.**

Funding **Braun Anaesthesia Scientific Research Fund and Wu Jieping Medical Foundation, Beijing, China. Study drugs were manufactured and supplied by Jiangsu Hengrui Medicine Co, Ltd, Jiangsu, China.**

Published **Online** August 16, 2015 http://dx.doi.org/10.1016/S0140-6736(16)30580-3

See **Online/Comment** http://dx.doi.org/10.1016/S0140-6736(16)31353-8

Department of Anaesthesiology and Critical Care Medicine (X Su MD, Z-T Meng MD, X-H Wu MD, F Cui MD, Prof D-X Wang MD), **Department of Biostatistics** (S N Zhu MS), **Peking University First Hospital, Beijing, China; Department of Critical Care Medicine, Peking University Third Hospital, Beijing, China** (H-L Li MD, Prof X Zhu MD); **Department of Anesthesia and Perioperative Care, University of California, San Francisco, CA, USA** (Prof M Maze MBChB); **and Section of Anaesthetics, Pain Management and Intensive Care, Department of Surgery and Cancer, Imperial College London, Chelsea and Westminster Hospital, London, UK** (Prof D Ma MD)

Correspondence to:
Prof Dong-Xin Wang, Department of Anaesthesiology and Critical Care Medicine, Peking University First Hospital, Beijing 100034, China
wangdongxin@hotmail.com

or

Prof Daqing Ma, Anaesthetics, Pain Medicine and Intensive Care, Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, Chelsea and Westminster Hospital, London, UK
d.ma@imperial.ac.uk

Introduction

A systematic review[1] revealed that postoperative delirium occurs in 11–51% of patients after surgery, and its prevalence increases with age. The occurrence of delirium is associated with increased morbidity and mortality, prolonged hospital stay, worse functional recovery, and long-term decline in cognitive function.[1,2] In patients admitted to hospital, around 30–40% of delirium cases are thought to be attributable to modifiable risk factors, and are therefore preventable.[3] Various approaches aimed at minimising the influence of risk factors in medical patients have not improved outcomes, and there are no conclusive studies that support pharmacological prophylaxis.[4]

Dexmedetomidine is a highly selective α_2 adrenoreceptor agonist that provides anxiolysis, sedation, and modest analgesia with minimal respiratory depression.[5] Dexmedetomidine is increasingly used for sedation in mechanically ventilated patients in the intensive care unit (ICU),[6] where its use is associated with a decreased prevalence of delirium when compared with other sedatives.[7,8] However, in each of these delirium-sparing studies,[7–9] dexmedetomidine was compared with an active sedative drug that modulates the γ-aminobutyric-acid type A ($GABA_A$) receptors. These modulators of $GABA_A$ receptors, exemplified by benzodiazepines, could increase the prevalence of delirium.[10] Another plausible explanation is that dexmedetomidine does not prevent the occurrence of delirium, but also does not increase the prevalence of delirium as do modulators of the $GABA_A$ receptors. Furthermore, the targeted patients were mechanically ventilated, which itself increases the risk of delirium.[11] Therefore, it is not clear whether dexmedetomidine has preventive effects against delirium in other patient populations, including non-ventilated patients. Lastly, the sedative dose of dexmedetomidine

Research in context

Evidence before this study

We searched PubMed between Jan 1, 2001, and Dec 31, 2015, with the terms of "dexmedetomidine", "postoperative delirium", and "elderly", and then limited to either "randomized controlled trial" or "meta-analysis". We identified seven small sample size randomised trials (three published in English and four in Chinese) and one meta-analysis. Dexmedetomidine was administered in five trials in a relatively high dose for sedation in postoperative patients. Of those, the primary endpoint was not the incidence or prevalence of delirium in three trials; in two trials published in Chinese, dexmedetomidine decreased the incidence of delirium during the first 3 days after oral cancer surgery in one trial while, in the other, patient-controlled analgesia supplemented with dexmedetomidine, given to elderly patients after spinal surgery, did not reduce the incidence of delirium during the first 3 postoperative days. The meta-analysis publication suggested that dexmedetomidine use in perioperative conditions or for intesive care unit (ICU) sedation is associated with a low risk of neurocognitive dysfunction.

Added value of this study

To our knowledge, this study is the first to suggest that prophylactic infusion of low-dose dexmedetomidine, an α_2 adrenoceptor agonist sedative, significantly decreases the prevalence of postoperative delirium without increase in adverse events.

Implications of all available evidence

The sub-sedative dose of dexmedetomidine can be safely used for elderly ICU patients after surgery, both with and without endotracheal intubation, to reduce the likelihood of postoperative delirium.

used in the earlier studies[9] was associated with an increase in hypotension or bradycardia, which limits a wider clinical application.[6] Because dexmedetomidine induces haemodynamic changes in a dose-dependent pattern,[12] it is important to define whether a lower dose than that used in other studies is still beneficial in decreasing delirium with fewer haemodynamic changes.

Sleep disturbances are common in postoperative patients, especially in those who are admitted to the ICU after major surgery,[13] and poor sleep is associated with a higher prevalence of postoperative delirium.[14] Results of a 2014 study[15] showed that night-time infusion of sedative dose dexmedetomidine improved sleep quality in mechanically ventilated ICU patients. With these results in mind, we did a feasibility study to test our hypothesis that low-dose dexmedetomidine infusion at a rate of 0·1 μg/kg per h could be beneficial for patients' sleep and beyond. We found that prophylactic infusion of low-dose dexmedetomidine improved the overall sleep quality measured by polysomnography and subjective assessment. This finding encouraged us to do a randomised controlled trial with a large sample size to investigate whether prophylactic intravenous infusion of low-dose dexmedetomidine decreases delirium in patients aged over 65 years (hereafter referred to as elderly patients) admitted to the ICU after non-cardiac surgery.

Methods

Study design

We did a randomised, double-blind, parallel-arm placebo-controlled trial in the ICUs of Peking University First Hospital and Peking University Third Hospital in Beijing, China. The study was designed to assess the superiority of the intervention. The study protocol (appendix) was approved by the local Clinical Research Ethics Committees (2011[10]). We obtained written informed consent from patients whose competence was established by their accurate orientation for time, place, and person, and understanding of the recruiter's description of the trial, or otherwise from their next of kin or their legal representative (appendix).

See Online for appendix

Patients

We screened potential participants on admission to the ICU. The inclusion criteria were patients aged 65 years or older who underwent elective non-cardiac surgery under general anaesthesia and were admitted to the ICU after surgery before 2000 h. Patients were excluded if they met any of the following criteria: preoperative history of schizophrenia, epilepsy, Parkinsonism, or myasthenia gravis; inability to communicate in the preoperative period (coma, profound dementia, or language barrier); brain injury or neurosurgery; known preoperative left ventricular ejection fraction less than 30%, sick sinus syndrome, severe sinus bradycardia (<50 beats per min [bpm]), or second-degree or greater atrioventricular block without pacemaker; serious hepatic dysfunction (Child-Pugh class C); serious renal dysfunction (undergoing dialysis before surgery); or low likelihood of survival for more than 24 h.

Randomisation and masking

A biostatistician, who was independent of data management and statistical analyses, generated random numbers (in a 1:1 ratio) using the SAS 9.2 software (SAS Institute, Cary, NC). The results of randomisation were sealed in sequentially numbered envelopes and stored at the site of investigation until the end of the study.

During the study period, consecutively recruited ICU patients were randomly assigned to receive either dexmedetomidine or placebo (normal saline). A study nurse administered the study drugs according to the randomisation sequence. Study personnel, health-care

team members, and patients were masked to the treatment group assignment throughout the study period. In an emergency (eg, unexpected, rapid deterioration in the patient's clinical status), intensivists could request unmasking of the treatment allocation, or adjust or interrupt study drug infusion if necessary. No unmasking occurred. These situations were documented, although analyses were done on the intention-to-treat population.

Procedures

Study drugs (dexmedetomidine hydrochloride 200 μg/2 mL and normal saline 2 mL) were provided as clear aqueous solutions in the same 3 mL bottles (manufactured by Jiangsu Hengrui Medicine Co, Ltd, Jiangsu, China) and dispensed according to the randomisation results by a pharmacist who did not participate in the rest of the study. The study drugs were diluted with normal saline to 50 mL (ie, dexmedetomidine hydrochloride final concentration was 4 μg/mL) before administration.

For patients who were not intubated, study drugs were given as a continuous intravenous infusion at a rate of 0·025 mL/kg per h (0·1 μg/kg per h of dexmedetomidine in the treatment group) from study recruitment on the day of surgery (usually within 1 h after ICU admission) until 0800 h on the first day after surgery. For those who were intubated and mechanically ventilated, the study drug infusion was started only after sedative (propofol or midazolam) administration was titrated to a Richmond Agitation Sedation Scale (RASS)[16] of –2 or higher (assessed hourly).

Postoperative analgesia was given with patient-controlled intravenous or epidural analgesia. For patients who did not receive patient-controlled analgesia or those who required analgesia in addition to that provided from patient-controlled dispensers, morphine or non-steroid anti-inflammatory drugs (flurbiprofen axetil) were given via intravenous infusion or bolus injection. Mechanically ventilated patients were sedated with propofol or midazolam via intravenous infusion or bolus injection, and morphine as necessary, titrated to achieve an RASS between –2 and +1 (assessed every 4 h). Daily sedation interruption was done for those who were not extubated by the morning of postoperative day 1. Patients were extubated when they met the following three criteria: adequate gas exchange during a spontaneous breathing trial, stable haemodynamic status (20% over or under baseline), and a level of consciousness associated with reflexes that protect the airway.

Several approaches to reduce the occurrence of delirium were instituted as part of standard operating procedures for patients in the ICU, including repeated reorientation, cognitive stimulation, early mobilisation, sleep-promotion strategies, hearing or vision aids, and timely correction of dehydration.[17] Patients who developed postoperative delirium were first given non-pharmacological strategies.[18] Haloperidol treatment was administered to those with severe agitation (RASS score of +3 or more) that was unresponsive to non-pharmacological therapy.[19] Enrolled patients were not to be given open-label dexmedetomidine; scopolamine and penehyclidine were prohibited; atropine was used only for the purpose of reversing bradycardia. ICU discharge was decided by the responsible intensivists; hospital discharge was decided by the responsible surgeons. Time of actual discharge was recorded.

Outcomes

Outcome assessment was done by research members who were trained before the study and not involved in the clinical care of patients. The primary endpoint was the incidence of delirium in the first 7 days after surgery. The first assessment of postoperative (also referred to as interval) delirium was done around 24 h after surgery;[20] we selected the timing of the first assessment to avoid diagnosing emergence delirium that can occur immediately after general anaesthesia and is not associated with adverse outcomes.[21,22] Twice daily (in the morning from 0800 h to 1000 h and in the evening from 1800 h to 2000 h) until the seventh day after surgery, we assessed delirium by the Confusion Assessment Method for the ICU (CAM-ICU); (appendix),[23] which has been validated in Chinese patients in the ICU setting[24] and the feasibility of which had been established in our other studies.[25,26] CAM-ICU addresses the four features of delirium, namely, acute onset of mental status changes or a fluctuating course, inattention, disorganised thinking, and altered level of consciousness. To achieve the diagnosis of delirium, a patient had to display acute onset of mental status changes or fluctuating course and inattention, with either disorganised thinking or altered level of consciousness. Immediately before assessing delirium, sedation or agitation was assessed using RASS. If the patient was too deeply sedated or unarousable (RASS –4 or –5), delirium assessment was aborted and the patient was recorded as comatose. If RASS was greater than –4 (–3 to +4), delirium was assessed by use of the CAM-ICU. Patients with delirium were classified into three motoric subtypes. Hyperactive delirium was defined when RASS was consistently positive (+1 to +4); hypoactive delirium was defined when RASS was consistently neutral or negative (–3 to 0); and mixed delirium was defined when some RASS scores were positive (+1 to +4) and some RASS scores were neutral or negative (–3 to 0).[27] For patients who were discharged or died within 7 days after surgery, the results of the last delirium assessment were considered the results of the missing data. These patients were excluded when calculating daily prevalence of delirium in a post-hoc analysis.

Secondary endpoints included time to extubation (from ICU admission to extubation), length of stay in the ICU (from ICU admission to ICU discharge), length of stay in the hospital after surgery (from day of surgery to hospital discharge), occurrence of non-delirium postoperative complications, and all-cause 30-day mortality. Non-delirium

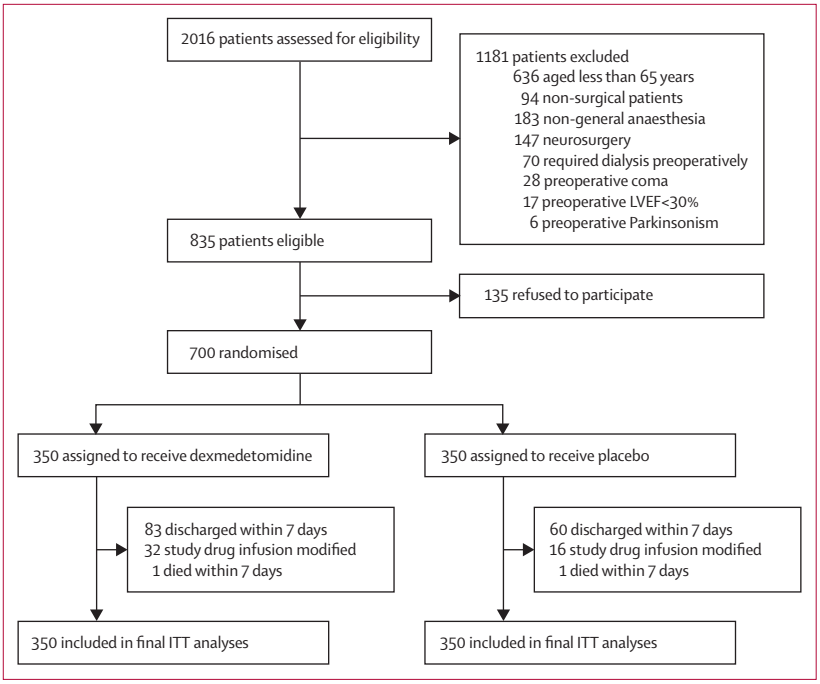

Figure 1: **Trial profile**
ITT analyses included all randomised patients in the groups to which they were randomly assigned. ITT=intention-to-treat. LVEF=left ventricular injection fraction.

complications were generally defined as medical events other than delirium that required therapeutic intervention and occurred within 30 days after surgery (appendix). Additional prespecified endpoints included postoperative pain intensity and subjective sleep quality. Pain intensity both at rest and with movement was assessed by use of the Numeric Rating Scale (NRS, an 11 point scale where 0 indicated no pain and 10 indicated the worst possible pain) at 3 h, 6 h, and 24 h after surgery. Subjective sleep quality was assessed by use of the NRS as well (an 11 point scale where 0 indicated the best possible sleep and 10 indicated the worst possible sleep)[28] at 0800 h on the first, second, and third days after surgery. Assessments of pain and sleep were only done if the RASS score was more than –4 (–3 to +4).

Adverse events were monitored until 24 h after surgery or until resolution of the event. Bradycardia was defined as heart rate less than 55 bpm or a decrease of more than 20% from baseline (in case of a baseline value [before study drug infusion] less than 69 bpm). Hypotension was defined as systolic blood pressure less than 95 mm Hg or a decrease of more than 20% from baseline (in case of a baseline value less than 119 mm Hg). Tachycardia was defined as heart rate greater than 100 bpm or an increase of more than 20% from baseline (in case of a baseline value greater than 83 bpm). Hypertension was defined as systolic blood pressure greater than 160 mm Hg or an increase of more than 20% from baseline (in case of a baseline value greater than 133 mm Hg). Hypoxaemia was defined as pulse oxygen saturation less than 90% or a decrease of more than 5% (absolute value) from baseline. Intervention for bradycardia, tachycardia, and hypertension included adjustment of study drug infusion or administration of medication, or both. Intervention for hypotension included adjustment of study drug infusion, intravenous fluid bolus, or administration of medication. Intervention for hypoxaemia included administration of oxygen (for patients without endotracheal intubation), adjustment of ventilator setting (for patients with endotracheal intubation), or physiotherapy.

Patients were followed up weekly after the first week until 30 days after surgery. All-cause 30-day mortality was recorded (appendix).

Statistical analysis

In our study, the incidence of postoperative delirium in a comparable patient population was 28%. In previous studies,[8,9] the incidence of delirium was reduced by roughly a third when dexmedetomidine was used in the ICU for sedating mechanically ventilated patients. Thus, we assumed that the incidence of delirium would be reduced by a third in the dexmedetomidine group in this study. With significance set at 0·05 and power set at 80%, the sample size required to detect differences was 656 patients, calculated with the Stata 10.0 software (StataCorp LP, College Station, TX, USA). Taking into account a loss-to-follow-up rate of about 6%, we planned to enrol 700 patients.

Numeric variables were analysed by use of an unpaired t test or Mann-Whitney u test. Categorical variables were analysed with the χ^2 test, continuity correction χ^2 test or likelihood ratio χ^2 test. The difference (and 95% CI for the difference) between two medians was calculated with the Hodges-Lehmann estimator. Time to event results were calculated with the Kaplan-Meier estimator, with differences between groups assessed by the log-rank test. Number needed to treat was estimated for the primary endpoint during a 7-day follow-up period. Because management of patients with or without endotracheal intubation on ICU admission is different, post-hoc subgroup analyses were also done.

We analysed outcome data and safety in the intention-to-treat population. We also did per-protocol analysis for the primary endpoint. We did not do an interim analysis. Statistical analyses were done on SPSS 14.0 software (SPSS, Chicago, IL) and SAS 9.2 software (SAS Institute, Cary, NC) with two-tailed tests wherever appropriate and p values less than 0·05 were considered to be of statistical significance. The Clinical Research Ethics Committee from Peking University First Hospital was involved in overseeing the data. The study is registered with www.chictr.org.cn, number ChiCTR-TRC-10000802.

Role of the funding source

The study sponsors had no role in study design, in the collection, analysis, and interpretation of data, or in the writing of the report. The corresponding authors had full

access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The corresponding authors have final responsibility for the decision to submit for publication.

Results

Between Aug 17, 2011, and Nov 20, 2013, 2016 patients were screened for study participation; of these, 700 patients were enrolled into the study and randomly assigned to receive either dexmedetomidine (n=350) or placebo (n=350); (figure 1). During the study period, there were no lapses in the blinding. Study drug infusion was modified in 48 patients because of adverse events. Delirium assessment was completed in all patients on the first day of ICU admission. No assessment was aborted because of deep sedation. 143 patients were discharged from the hospital within 7 days after surgery. Two patients died, both on postoperative day 2 (one patient in each group). All patients were included in the final intention-to-treat analyses (figure 1). The final visit of the last randomised patient was done on Dec 20, 2013.

Overall, the two groups were well matched for baseline and perioperative variables, except that the percentage of patients with preoperative renal dysfunction (serum creatinine greater than 177 μmol/L) was lower in the dexmedetomidine group than in the placebo group and the percentage of patients who required intraoperative blood transfusion was less in the dexmedetomidine group than in the placebo group (table 1 and appendix). After randomisation, a similar proportion of patients received supplemental sedation in both groups. However, among patients who received propofol sedation (for mechanical ventilation) after surgery, the total dose of propofol given was less in the dexmedetomidine group than in the placebo group (table 1).

Postoperative delirium occurred in 79 (23%) of 350 patients given placebo, and in 32 (9%) of 350 patients given dexmedetomidine (odds ratio [OR] 0·35, 95% CI 0·22–0·54; p<0·0001), with number needed to treat of 7·4 (95% CI 5·3–12·3) during 7-day follow-up. Per-protocol analysis also showed a similar difference in the prevalence of delirium between groups (74 [22%] of 334 patients given placebo *vs* 29 [9%] of 318 patients given dexmedetomidine, OR 0·35; 95% CI 0·22–0·56, p<0·0001). Post-hoc analyses showed that daily prevalence of delirium was significantly lower in the dexmedetomidine group than in the placebo group on postoperative days 1–3 (day 1: 0·28, 0·16–0·50; p<0·0001, day 2: 0·43, 0·24–0·77; p=0·005, day 3: 0·26, 0·13–0·53; p<0·0001, figure 2). The reduction in the incidence of delirium remained when patients were stratified according to the intubation status on ICU admission (table 2). Each of the three motoric subtypes of delirium was significantly decreased in the dexmedetomidine group (p<0·0001). The delirium-sparing effect of low-dose dexmedetomidine became significant when the duration of infusion was 12·25 h or longer (table 2).

	Placebo group (n=350)	Dexmedetomidine group (n=350)
Benzodiazepine use in preoperative night	39 (11·1%)	40 (11·4%)
Type of anaesthesia		
General	290 (82·9%)	288 (82·3%)
Combined epidural-general	60 (17·1%)	62 (17·7%)
Intraoperative medication		
Midazolam	173 (49·4%)	153 (43·7%)
Dexamethasone*	260 (74·3%)	262 (74·9%)
Other glucocorticoids	80 (22·9%)	77 (22·0%)
Atropine†	36 (10·3%)	38 (10·9%)
Duration of anaesthesia (min)	320 (156)	307 (135)
Surgery for malignant tumour	252 (72·0%)	274 (78·3%)
Type of surgery		
Intra-abdominal	235 (67·1%)	240 (68·6%)
Intra-thoracic	56 (16·0%)	64 (18·3%)
Spinal and extremital	24 (6·9%)	12 (3·4%)
Superficial and transurethral	35 (10·0%)	34 (9·7%)
Duration of surgery (min)	238 (148)	219 (124)
Estimated blood loss during surgery (mL)	250 (100–600)	200 (100–500)
Blood transfusion during surgery	67 (19·1%)	47 (13·4%)
Total intraoperative infusion (mL)	2600 (1600–4100)	2400 (1600–3600)
Patients with endotracheal intubation on ICU admission	191 (54·6%)	191 (54·6%)
APACHE II score on ICU admission (score)	10·6 (3·9)	10·2 (3·3)
Duration of study drug infusion (h)	14·56 (3·40)	14·95 (3·30)
Postoperative analgesia		
None	34 (9·7%)	39 (11·1%)
Patient-controlled intravenous analgesia‡	264 (75·4%)	252 (72·0%)
Patient-controlled epidural analgesia§	52 (14·9%)	59 (16·9%)
Use of other analgesics or sedatives during the first 7 postoperative days		
Propofol	178 (50·9%)	179 (51·1%)
Propofol (mg)¶	275 (120–530)	200 (120–400)
Flurbiprofen axetil	110 (31·4%)	116 (33·1%)
Flurbiprofen axetil (mg)¶	100 (50–100)	100 (62·5–150)
Morphine	102 (29·1%)	99 (28·3%)
Morphine (mg)¶	3·5 (2–6)	4 (2–7)
Midazolam	34 (9·7%)	24 (6·9%)
Midazolam (mg)¶	2·5 (1–6·1)	4 (2–10)

Data are number (%), mean (SD), or median (interquartile range). ICU=intensive care unit. APACHE II=Acute Physiology and Chronic Health Evaluation II score. *For prophylaxis of postoperative nausea and vomiting· †Administered in combination with neostigmine, for reversal of residual neuromuscular blockade. ‡Established with 100 mL of 0·5 mg/mL morphine or 1·25 μg/mL sufentanil, programmed to deliver a 2 mL bolus with a lockout interval of 6–10 min and a background infusion of 1 mL/h. §Established with 250 mL of 0·12% ropivacaine plus 0·5 μg/mL sufentanil, programmed to deliver a 2 mL bolus with a lockout interval of 20 min and a background infusion of 4 mL/h. ¶Dosage among patients who had received the drugs.

***Table 1*: Perioperative variables**

For patients with endotracheal intubation on ICU admission, median time to extubation was longer in the placebo group than in the dexmedetomidine group (6·9 h [95% CI 5·2–8·6] with placebo and 4·6 h [3·4–5·8] with dexmedetomidine [hazard ratio (HR) 1·25, 95% CI 1·02–1·53; p=0·031]). For all patients, the aggregate prevalence of non-delirium complications was reduced from 73 (21%) of 350 patients given placebo to 52 (15%)

of 350 patients given dexmedetomidine (OR 0·66, 95% CI 0·45–0·98; p=0·039) (appendix), the length of stay in the ICU was longer in the placebo group, at 21·5 h (20·7–22·3) than with dexmedetomidine (20·9 h [20·4–21·4]; HR 1·18, 1·02–1·37; p=0·027); no significant differences between the two groups were seen in length of stay in hospital after surgery and all-cause 30-day mortality. However, in a post-hoc analysis, the percentage of patients who were discharged from hospital within 7 days after surgery was higher in the dexmedetomidine group (83 [24%] of 350 patients) than in the placebo group (60 [17%] of 350 patients, OR 1·50; 1·04–2·18, p=0·032; table 2).

The NRS pain scores both at rest and with movement were significantly lower in the dexmedetomidine group than in the placebo group at 3, 6, and 24 h after surgery (all p<0·0001, except for one p=0·001 at 24 h with movement); however, the mean difference of NRS pain score between groups was small (0 to –1). The NRS scores of subjective sleep quality were also significantly lower (ie, better) in the dexmedetomidine group than in the placebo group at 0800 h on the first, second, and third days after surgery (all p<0·0001; table 2).

The RASS scores at the end of study drug infusion were similar between the two groups. Incidence of bradycardia and hypotension did not differ between groups, or the percentage of patients requiring intervention for these adverse events. On the other hand, the incidence of tachycardia (p=0·002), hypertension (p=0·002), and hypoxaemia (p=0·001) were significantly lower, and, accordingly, the percentages of patients who required intervention for tachycardia (p=0·005) and hypertension (p=0·016) were significantly less in the dexmedetomidine group than in the placebo group. However, the percentages of patients in whom the study drug infusion was modified (infusion rate decreased, or infusion interrupted temporarily or permanently) were significantly greater (p=0·046) in the dexmedetomidine group than in the placebo group (table 3).

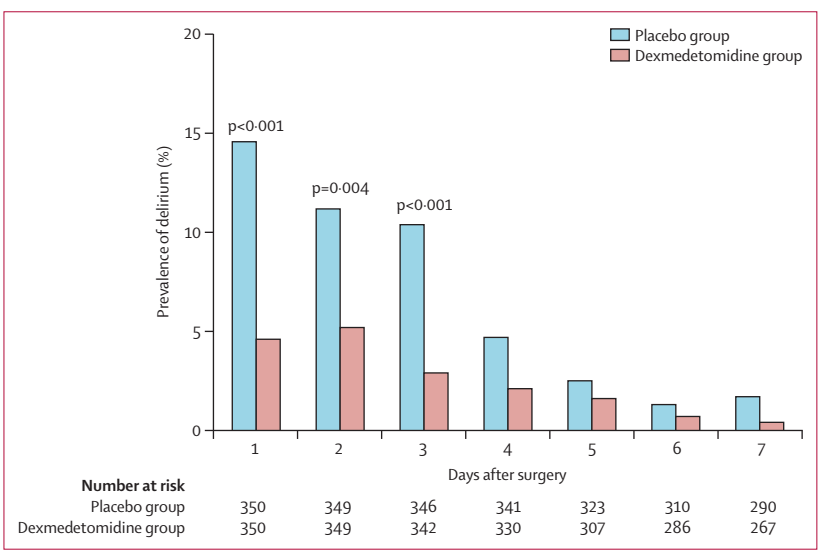

***Figure 2*: Daily prevalence of postoperative delirium**
Sample sizes differ from the first to seventh day because some patients were discharged from hospital or died during this period.

Discussion

Our results suggest that a prophylactic low-dose dexmedetomidine infusion significantly decreases the incidence of delirium in the first 7 days after surgery in elderly patients admitted to the ICU after non-cardiac surgery. This conclusion seems to be true for patients with or without endotracheal intubation on ICU admission and for all three motoric subtypes of delirium. Dexmedetomidine also significantly improves the subjective quality of sleep, decreases the prevalence of non-delirium complications, shortens the length of stay in the ICU, and increases the percentage of early hospital discharge, but does not significantly increase adverse events. To our knowledge, ours is the first sufficiently powered randomised study that shows the benefit of low-dose dexmedetomidine infusion in this surgical patient population.

Postoperative delirium developed in 23% of patients in the placebo group, similar to previous studies.[1,11,25] In keeping with previous reports, the prevalence of postoperative delirium was higher in the patients with endotracheal intubation on ICU admission than in those without.[29] This difference might be due to a more severe underlying condition in intubated patients on ICU admission, which is associated with an increased risk of postoperative delirium.[30] Secondly, our protocol permitted the use of supplemental sedatives or analgesics in mechanically ventilated patients during ICU stay; consequently more of these patients received supplemental propofol, midazolam, and morphine, each of which might increase the risk of postoperative delirium.[31]

Dexmedetomidine has been used by intensivists in general practice for sedation in mechanically ventilated ICU patients at an infusion rate from 0·2 to 1·7 μg/kg per h with or without a loading dose;[7–9] these sedative doses of dexmedetomidine are associated with adverse events, especially hypotension and bradycardia.[7–9] In this study, patients were not given a loading dose of dexmedetomidine, and a sub-sedative infusion rate (ie, 0·1 μg/kg per h) was given. The RASS scores were similar between the two groups, indicating that low-dose dexmedetomidine did not produce significant sedation. Our protocol was designed to ensure a period of study drug infusion from ICU admission on the day of surgery until 0800 h on the first postoperative morning for a number of reasons. Firstly, any prophylactic pharmacological intervention should be initiated early because the prevalence of delirium is at its highest during the early postoperative hours.[30] Secondly, study drug infusion should cover the night-time hours, to improve patients' sleep quality, since dexmedetomidine's central action converges on the endogenous sleep-promoting pathway.[32] Thirdly, we anticipated that about half of the elective

	Placebo group (n=350)	Dexmedetomidine group (n=350)	OR, HR, or difference (95% CI)	p value
Primary endpoint				
Overall incidence of delirium*	79 (22·6%)	32 (9·1%)	OR=0·35 (0·22 to 0·54)	<0·0001
Secondary endpoints				
Time to extubation† (h)	6·9 (5·2 to 8·6) (n = 191)	4·6 (3·4 to 5·8) (n = 191)	HR=1·25 (1·02 to 1·53)	0·031
Overall incidence of non-delirium complications‡	73 (20·9%)	52 (14·9%)	OR=0·66 (0·45 to 0·98)	0·039
Length of stay in ICU (h)	21·5 (20·7 to 22·3)	20·9 (20·4 to 21·4)	HR=1·18 (1·02 to 1·37)	0·027
Length of stay in hospital after surgery (day)	11·0 (10·2 to 11·8)	10·0 (9·2 to 10·8)	HR=1·09 (0·94 to 1·27)	0·24
All-cause 30-day mortality	4 (1·1%)	1 (0·3%)	OR=0·25 (0·03 to 2·23)	0·21
Prespecified analyses				
NRS for pain at rest§ (score)				
3 h after surgery	2 (1 to 4)	2 (0 to 3)	D=0 (–1 to 0)	<0·0001
6 h after surgery	2 (1 to 3)	1 (0 to 2)	D=–1 (–1 to 0)	<0·0001
24 h after surgery	1 (0 to 3)	1 (0 to 2)	D=0 (–1 to 0)	<0·0001
NRS for pain with movement§ (score)				
3 h after surgery	3 (2 to 5)	3 (2 to 4)	D=–1 (–1 to 0)	<0·0001
6 h after surgery	3 (2 to 4)	2 (1 to 3)	D=–1 (–1 to 0)	<0·0001
24 h after surgery	2 (1 to 4)	2 (1 to 3)	D=0 (–1 to 0)	0·001
NRS for subjective sleep quality§ (score)				
First morning after surgery	4 (2 to 6)	2 (0 to 4)	D=–2 (–2 to –2)	<0·0001
Second morning after surgery	4 (2 to 6)	2 (1 to 5)	D=–1 (–1 to –1)	<0·0001
Third morning after surgery	4 (2 to 5)	2 (0 to 4)	D=–1 (–2 to –1)	<0·0001
Exploratory analyses				
Time to onset of delirium (day)	5·8 (5·5 to 6·0)	6·5 (6·4 to 6·7)	HR=0·39 (0·26 to 0·58)	<0·0001
Incidence of delirium according to intubation status on ICU admission				
With endotracheal intubation	55 (28·8%) (n=191)	22 (11·5%) (n=191)	OR=0·32 (0·19 to 0·55)	<0·0001
Without endotracheal intubation	24 (15·1%) (n=159)	10 (6·3%) (n=159)	OR=0·38 (0·17 to 0·82)	0·014
Incidence of delirium according to duration of study drug infusion¶				
<12·25 h	17 (18·3%) (n=93)	11 (14·3%) (n=82)	OR=0·75 (0·33 to 1·70)	0·49
≥12·25 but <15·00 h	17 (25·0%) (n=68)	7 (10·3%) (n=68)	OR=0·34 (0·13 to 0·90)	0·029
≥15·00 but <17·58 h	26 (24·3%) (n=107)	7 (6·3%) (n=111)	OR=0·21 (0·09 to 0·51)	0·001
≥17·58 h	19 (23·2%) (n=82)	7 (7·4%) (n=94)	OR=0·27 (0·11 to 0·67)	0·005
Motoric subtype of delirium				<0·0001
None	271 (77·4%)	318 (90·9%)	..	..
Hypoactive	42 (12·0%)	20 (5·7%)	..	..
Hyperactive	13 (3·7%)	3 (0·9%)	..	..
Mixed	24 (6·9%)	9 (2·6%)	..	..
Haloperidol treatment	2 (0·6%)	1 (0·3%)	OR=0·50 (0·05 to 5·52)	>0·99
Time to onset of non-delirium complications (days)	24·6 (23·5 to 25·7)	26·3 (25·4 to 27·3)	HR=0·68 (0·48 to 0·98)	0·036
Discharge from hospital within 7 days after surgery	60 (17·1%)	83 (23·7%)	OR=1·50 (1·04 to 2·18)	0·032

Data are number (%) or median (95% CI) unless indicated otherwise. OR=odds ratio. HR=hazard ratio. ICU=intensive care unit. NRS=numeric rating scale. D=difference. *Occurrence of delirium at any time during the first 7 days after surgery. †Result of patients who were admitted to the ICU with endotracheal intubation. ‡Occurrence of any non-delirium complications within 30 days after surgery. §Data are median (IQR). ¶Stratified according to quartiles of the duration.

***Table 2*: Effectiveness outcomes**

surgical population that require ICU admission would be discharged from the ICU within 24 h; by terminating infusion of dexmedetomidine at 0800 h on the first postoperative day, enough time has elapsed to enable a drug with a terminal elimination half-life of 3·7 h to be cleared from the plasma by the time the patient is discharged from the ICU.[33]

Although results of previous studies[7–9,31] showed that the occurrence of delirium was reduced in patients randomly assigned to receive sedative-inducing doses of dexmedetomidine versus an alternative sedative-hypnotic (benzodiazepines or propofol) or analgesic (opiates) in mechanically ventilated patients, it was unclear whether those patients benefited through a prophylactic action of dexmedetomidine, or by avoiding delirium-inducing sedatives and analgesics. Our study was placebo-controlled, and a similar proportion of patients received supplemental sedation in both groups, although

	Placebo (n=350)	Dexmedetomidine (n=350)	p value
RASS score at the end of study drug infusion (scale)	0 (0 to –1)	0 (0 to –2)	0·12
Adverse events			
Bradycardia	46 (13·1%)	59 (16·9%)	0·17
Bradycardia with intervention	1 (0·3%)	5 (1·4%)	0·22
Hypotension	92 (26·3%)	114 (32·6%)	0·07
Hypotension with intervention	32 (9·1%)	34 (9·7%)	0·80
Tachycardia	48 (13·7%)	23 (6·6%)	0·002
Tachycardia with intervention	25 (7·1%)	9 (2·6%)	0·005
Hypertension	62 (17·7%)	34 (9·7%)	0·002
Hypertension with intervention	19 (5·4%)	7 (2·0%)	0·016
Hypoxaemia	50 (14·3%)	24 (6·9%)	0·001
Hypoxaemia with intervention	3 (0·9%)	0 (0·0%)	0·25
Modification of study drug infusion*			0·046
None	334 (95·4%)	318 (90·9%)	..
Infusion rate decreased temporarily	1 (0·3%)	5 (1·4%)	..
Infusion stopped temporarily	14 (4·0%)	22 (6·3%)	..
Infusion stopped permanently	1 (0·3%)	5 (1·4%)	..

Data are median (full range) or n (%). RASS=Richmond Agitation Sedation Scale. *Study drug infusion was modified by the attending intensivists before the scheduled end.

***Table 3*: Safety outcomes**

the total consumed propofol dose was less in the patients who received dexmedetomidine (table 1). Additionally, post-hoc subgroup analysis showed that dexmedetomidine was efficacious in preventing postoperative delirium in both the intubated and non-intubated patients. Although the absolute effect size for the delirium-reducing improvement was higher in the intubated patients, the improvement was quite similar (table 2). Importantly, our data also showed that the delirium-sparing effect of low-dose dexmedetomidine is dose-dependent, because there is a significant negative correlation between the amount of dexmedetomidine given (infusion duration multiplied by rate) and the probability of developing delirium (Pearson correlation coefficient –0·190, p<0·0001). Moreover, dexmedetomidine's effect in preventing delirium was not limited to the period of drug infusion but extended up to the third postoperative day (figure 2). Collectively, taking this investigation together with previous studies, one can state with greater confidence that the inclusion of dexmedetomidine was the reason for the delirium-reducing effect.

Dexmedetomidine significantly decreased hypoxaemia in our patients; results of other studies[14,34] have showed that postoperative hypoxaemia independently contributes to the development of delirium. The underlying mechanism for dexmedetomidine's hypoxaemia-sparing action was not directly investigated; preclinical studies highlight its pulmonary protective effect after remote organ injury.[35] However, this apparent effect could also just be a coincident significant finding and warrants further study.

Dexmedetomidine can provide analgesia by acting on the α_2 adrenergic receptors in the spinal cord.[36,37] Our results also showed that a lower dose of dexmedetomidine significantly decreased postoperative NRS pain score for up to 24 h after surgery. However, this decrease is small and, therefore, unlikely to have clinical significance. Nevertheless, pain itself is a risk factor for the development of delirium,[38] so a delirium-sparing pharmacoprophylaxis would seem to be a better strategy than increasing putative delirium-enhancing analgesic drugs to combat postoperative pain.

Results of this study show that dexmedetomidine infusion significantly improves the subjective sleep quality of postoperative ICU patients, and this benefit persists beyond the period of drug infusion, ie, for 3 postoperative days, which is consistent with significant reduction in daily delirium prevalence. Dexmedetomidine exerts hypnotic properties by activating the endogenous sleep-promoting pathway and produces a stage II non-rapid eye movement sleep-like state.[32] In mechanically ventilated ICU patients, night-time infusion of dexmedetomidine (0·2–0·7 μg/kg per h) preserved day–night sleep cycles.[39] We speculated that producing a state akin to natural sleep with dexmedetomidine would be a better strategy than delirium-enhancing sedative-hypnotics, such as benzodiazepines, that produce an immobilised state that is unlike natural sleep.[40]

Apart from the dexmedetomidine-induced improvements in hypoxaemia, analgesia, and sleep in this study, a possible mechanism for dexmedetomidine's postoperative delirium-reducing property might also be attributed to its actions on inflammation that are evident both clinically[41] and in preclinical models.[42] A strong association has been shown between elevated biomarkers of inflammation and the risk for developing delirium;[43] the causal nature of this relationship has been repeatedly shown in preclinical studies.[44,45] As biomarkers of inflammation were not measured it is not possible to assess whether low-dose dexmedetomidine infusion suppresses the inflammation associated with the aseptic trauma of surgery.

In respect of safety, our data reveal that dexmedetomidine-induced bradycardia and hypotension were not significantly increased, possibly because of the very low doses that were used, whereas hypertension and tachycardia were both significantly decreased in patients given dexmedetomidine. However, our study was powered for efficacy, but not safety; a larger-scale study will be required to rule out possible safety concerns. Nevertheless, the haemodynamic-stabilising property of dexmedetomidine might be beneficial, as this property reduces adverse cardiac events in high-risk patients.[46] Although we did not observe significant differences in cardiovascular events in the present study, the overall prevalence of postoperative complications was significantly lower in the dexmedetomidine group.

In line with previous reports,[47] our data showed that dexmedetomidine shortened the duration of mechanical

ventilation and the length of ICU stay, and increased the percentage of early hospital discharge. The previously discussed effects produced by dexmedetomidine infusion, including enhanced haemodynamic stability and lowered prevalence of delirium and non-delirium complications, could each contribute to these results.[48] However, our study does not provide causal relationships between the various concurrent outcomes. In line with our data, a small study[49] showed that dexmedetomidine decreases time to extubation in mechanically ventilated ICU patients who have agitated delirium.

Although our pragmatic study has many strengths, including enrolment of a sufficiently large sample size (700 surgical patients) to achieve significant differences in the primary endpoints and some of the secondary endpoints between the two groups, there are several limitations. First, the ICU is a noisy and task-intensive environment that places patients at risk for delirium through sleep deprivation and sleep fragmentation. As we only enrolled ICU surgical patients, it is not certain that low-dose dexmedetomidine infusion will lessen sleep disruptions and thereby decrease delirium in postoperative patients in non-ICU settings or medical patients in the ICU. Second, all participants were screened and enrolled after ICU admission and did not have baseline delirium assessment with cognitive function assessment. Therefore, we cannot preclude the potential bias introduced by preoperative imbalance of baseline conditions. However, strict randomisation and large sample size should have helped to balance these factors between groups. Third, despite strict randomisation, some baseline and perioperative parameters were not well balanced between the two groups, a not uncommon feature in randomised controlled trials. Therefore, we cannot preclude the potential bias produced by imbalance of these factors. Lastly, it has been noted that CAM-ICU might not be as sensitive as other tools, eg, 3D-CAM, for delirium assessment especially for other ethnic groups[50,51] and in non-ICU settings.[52]

Our study indicates that, in elderly patients admitted to the ICU after non-cardiac surgery, prophylactic low-dose dexmedetomidine infusion significantly decreases the prevalence of postoperative delirium. The administration of low-dose dexmedetomidine did not significantly increase the prevalence of bradycardia or hypotension, but significantly decreased the prevalence of hypertension, tachycardia, and hypoxaemia. However, whether the favourable effects afforded by this novel application of dexmedetomidine result in improved long-term outcomes remains unknown.

Contributors

D-XW, Z-TM, and DM contributed to the study concept and design. XS, Z-TM, X-HW, FC, and H-LL contributed to acquisition of data. XS, Z-TM, D-XW, XZ, and S-NZ analysed and interpreted the data. XS drafted the manuscript. D-XW, DM, and MM critically revised the manuscript for intellectual content. S-NZ, XS, and D-XW contributed to statistical analysis. D-XW supplied administrative, technical, and material support. Z-TM and D-XW were responsible for study supervision.

Declaration of interests

D-XW reports lecture fees and travel expenses for lectures given at domestic academic meetings from Pfizer China, AstraZeneca China, Jiangsu Hengrui Medicine Co Ltd, China, and Yichang Humanwell Pharmaceutical Co Ltd, China. MM is supported by National Institutes of Health R01GM104194, Bethesda, MA, USA. DM is supported by grants from the British Oxygen Chair, and British Journal of Anaesthesia Fellowship, London, UK. The other authors declare no competing interests. Part of the work was presented at the 27th Annual Congress of European Society of Intensive Care Medicine (ESICM), 2014 in Barcelona, Spain.

Acknowledgments

The authors gratefully acknowledge Xin-Yu Sun (Department of Psychiatrics, Peking University Sixth Hospital, Beijing, China) for her help in psychiatric consultation. The authors also thank Alex S Evers (Washington of University School of Medicine, St Louis, USA) for his critical comments during manuscript preparation.

References

1 Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet* 2014; **383:** 911–22.
2 Abelha FJ, Luis C, Veiga D, et al. Outcome and quality of life in patients with postoperative delirium during an ICU stay following major surgery. *Crit Care* 2013; **17:** R257.
3 Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. *Age Ageing* 2006; **35:** 350–64.
4 Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med* 2013; **41:** 263–306.
5 Mo Y, Zimmermann AE. Role of dexmedetomidine for the prevention and treatment of delirium in intensive care unit patients. *Ann Pharmacother* 2013; **47:** 869–76.
6 Wunsch H, Kahn JM, Kramer AA, et al. Dexmedetomidine in the care of critically ill patients from 2001 to 2007: an observational cohort study. *Anesthesiology* 2010; **113:** 386–94.
7 Pandharipande PP, Pun BT, Herr DL, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA* 2007; **298:** 2644–53.
8 Xia ZQ, Chen SQ, Yao X, Xie CB, Wen SH, Liu KX. Clinical benefits of dexmedetomidine versus propofol in adult intensive care unit patients: a meta-analysis of randomized clinical trials. *J Surg Res* 2013; **185:** 833–43.
9 Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA* 2009; **301:** 489–99.
10 Fraser GL, Devlin JW, Worby CP, et al. Benzodiazepine versus nonbenzodiazepine-based sedation for mechanically ventilated, critically ill adults: a systematic review and meta-analysis of randomized trials. *Crit Care Med* 2013; **41:** S30–38.
11 Vasilevskis EE, Han JH, Hughes CG, Ely EW. Epidemiology and risk factors for delirium across hospital settings. *Best Pract Res Clin Anaesthesiol* 2012; **26:** 277–87.
12 Bloor BC, Ward DS, Belleville JP, Maze M. Effects of intravenous dexmedetomidine in humans. II. Hemodynamic changes. *Anesthesiology* 1992; **77:** 1134–42.
13 Rosenberg J. Sleep disturbances after non-cardiac surgery. *Sleep Med Rev* 2001; **5:** 129–37.
14 Flink BJ, Rivelli SK, Cox EA, et al. Obstructive sleep apnea and incidence of postoperative delirium after elective knee replacement in the nondemented elderly. *Anesthesiology* 2012; **116:** 788–96.
15 Alexopoulou C, Kondili E, Diamantaki E, et al. Effects of dexmedetomidine on sleep quality in critically ill patients: a pilot study. *Anesthesiology* 2014; **121:** 801–07.
16 Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 2002; **166:** 1338–44.
17 Inouye SK, Bogardus ST Jr, Williams CS, Leo-Summers L, Agostini JV. The role of adherence on the effectiveness of nonpharmacologic interventions: evidence from the delirium prevention trial. *Arch Intern Med* 2003; **163:** 958–64.
18 Inouye SK. Delirium in older persons. *N Engl J Med* 2006; **354:** 1157–65.

19 Cole MG. Delirium in elderly patients. *Am J Geriatr Psychiatry* 2004; **12:** 7–21.

20 Silverstein JH, Timberger M, Reich DL, Uysal S. Central nervous system dysfunction after noncardiac surgery and anesthesia in the elderly. *Anesthesiology* 2007; **106:** 622–28.

21 Kim HJ, Kim DK, Kim HY, Kim JK, Choi SW. Risk factors of emergence agitation in adults undergoing general anesthesia for nasal surgery. *Clin Exp Otorhinolaryngol* 2015; **8:** 46–51.

22 Munk L, Andersen G, Moller AM. Post-anaesthetic emergence delirium in adults: incidence, predictors and consequences. *Acta Anaesthesiol Scand* 2016; published online March 10. DOI:10.1111/aas.12717.

23 Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA* 2001; **286:** 2703–10.

24 Wang C, Wu Y, Yue P, et al. Delirium assessment using Confusion Assessment Method for the Intensive Care Unit in Chinese critically ill patients. *J Crit Care* 2013; **28:** 223–29.

25 Wang W, Li HL, Wang DX, et al. Haloperidol prophylaxis decreases delirium incidence in elderly patients after noncardiac surgery: a randomized controlled trial. *Crit Care Med* 2012; **40:** 731–39.

26 Mu DL, Wang DX, Li LH, et al. High serum cortisol level is associated with increased risk of delirium after coronary artery bypass graft surgery: a prospective cohort study. *Crit Care* 2010; **14:** R238.

27 Peterson JF, Pun BT, Dittus RS, et al. Delirium and its motoric subtypes: a study of 614 critically ill patients. *J Am Geriatr Soc* 2006; **54:** 479–84.

28 Ritmala-Castren M, Lakanmaa RL, Virtanen I, Leino-Kilpi H. Evaluating adult patients' sleep: an integrative literature review in critical care. *Scand J Caring Sci* 2014; **28:** 435–48.

29 Burkhart CS, Dell-Kuster S, Gamberini M, et al. Modifiable and nonmodifiable risk factors for postoperative delirium after cardiac surgery with cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 2010; **24:** 555–59.

30 Shi CM, Wang DX, Chen KS, Gu XE. Incidence and risk factors of delirium in critically ill patients after non-cardiac surgery. *Chin Med J (Engl)* 2010; **123:** 993–99.

31 Reade MC, Finfer S. Sedation and delirium in the intensive care unit. *N Engl J Med* 2014; **370:** 444–54.

32 Nelson LE, Lu J, Guo T, Saper CB, Franks NP, Maze M. The alpha2-adrenoceptor agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects. *Anesthesiology* 2003; **98:** 428–36.

33 Iirola T, Aantaa R, Laitio R, et al. Pharmacokinetics of prolonged infusion of high-dose dexmedetomidine in critically ill patients. *Crit Care* 2011; **15:** R257.

34 Bilotta F, Lauretta MP, Borozdina A, Mizikov VM, Rosa G. Postoperative delirium: risk factors, diagnosis and perioperative care. *Minerva Anestesiol* 2013; **79:** 1066–76.

35 Gu J, Chen J, Xia P, Tao G, Zhao H, Ma D. Dexmedetomidine attenuates remote lung injury induced by renal ischemia-reperfusion in mice. *Acta Anaesthesiol Scand* 2011; **55:** 1272–78.

36 Chrysostomou C, Schmitt CG. Dexmedetomidine: sedation, analgesia and beyond. *Expert Opin Drug Metab Toxicol* 2008; **4:** 619–27.

37 Lin TF, Yeh YC, Lin FS, et al. Effect of combining dexmedetomidine and morphine for intravenous patient-controlled analgesia. *Br J Anaesth* 2009; **102:** 117–22.

38 Kosar CM, Tabloski PA, Travison TG, et al. Effect of preoperative pain and depressive symptoms on the development of postoperative delirium. *Lancet Psychiatry* 2014; **1:** 431–36.

39 Oto J, Yamamoto K, Koike S, Onodera M, Imanaka H, Nishimura M. Sleep quality of mechanically ventilated patients sedated with dexmedetomidine. *Intensive Care Med* 2012; **38:** 1982–89.

40 Coull JT, Jones ME, Egan TD, Frith CD, Maze M. Attentional effects of noradrenaline vary with arousal level: selective activation of thalamic pulvinar in humans. *Neuroimage* 2004; **22:** 315–22.

41 Memis D, Hekimoglu S, Vatan I, Yandim T, Yuksel M, Sut N. Effects of midazolam and dexmedetomidine on inflammatory responses and gastric intramucosal pH to sepsis, in critically ill patients. *Br J Anaesth* 2007; **98:** 550–52.

42 Xiang H, Hu B, Li Z, Li J. Dexmedetomidine controls systemic cytokine levels through the cholinergic anti-inflammatory pathway. *Inflammation* 2014; **37:** 1763–70.

43 Capri M, Yani SL, Chattat R, et al. Pre-operative, high-IL-6 blood level is a risk factor of post-operative delirium onset in old patients. *Front Endocrinol (Lausanne)* 2014; **5:** 173.

44 Wan Y, Xu J, Ma D, Zeng Y, Cibelli M, Maze M. Postoperative impairment of cognitive function in rats: a possible role for cytokine-mediated inflammation in the hippocampus. *Anesthesiology* 2007; **106:** 436–43.

45 Terrando N, Eriksson LI, Ryu JK, et al. Resolving postoperative neuroinflammation and cognitive decline. *Ann Neurol* 2011; **70:** 986–95.

46 Chalikonda SA. Alpha2-adrenergic agonists and their role in the prevention of perioperative adverse cardiac events. *AANA J* 2009; **77:** 103–08.

47 Pasin L, Greco T, Feltracco P, et al. Dexmedetomidine as a sedative agent in critically ill patients: a meta-analysis of randomized controlled trials. *PLoS One* 2013; **8:** e82913.

48 Voga G. Hemodynamic changes during weaning: can we assess and predict cardiac-related weaning failure by transthoracic echocardiography? *Crit Care* 2010; **14:** 174.

49 Reade MC, Eastwood GM, Bellomo R, et al. Effect of dexmedetomidine added to standard care on ventilator-free time in patients with agitated delirium: a randomized clinical trial. *JAMA* 2016; **315:** 1460–68.

50 Nishimura K, Yokoyama K, Yamauchi N, et al. Sensitivity and specificity of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) for detecting post-cardiac surgery delirium: a single-center study in Japan. *Heart Lung* 2016; **45:** 15–20.

51 van Eijk MM, van den Boogaard M, van Marum RJ, et al. Routine use of the confusion assessment method for the intensive care unit: a multicenter study. *Am J Respir Crit Care Med* 2011; **184:** 340–44.

52 Kuczmarska A, Ngo LH, Guess J, et al. Detection of delirium in hospitalized older general medicine patients: a comparison of the 3D-CAM and CAM-ICU. *J Gen Intern Med* 2016; **31:** 297–303.