Randomized clinical trial

Randomized clinical trial of intraoperative dexmedetomidine to prevent delirium in the elderly undergoing major non-cardiac surgery

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Background: **Delirium is common in elderly patients after surgery and is associated with poor outcomes. This study aimed to investigate the impact of intraoperative dexmedetomidine on the incidence of delirium in elderly patients undergoing major surgery.**

Methods: **This was a randomized double-blind placebo-controlled trial. Elderly patients (aged 60 years or more) scheduled to undergo major non-cardiac surgery were randomized into two groups. Patients in the intervention group received a loading dose of dexmedetomidine 0·6 μg/kg 10 min before induction of anaesthesia followed by a continuous infusion (0·5 μg per kg per h) until 1 h before the end of surgery. Patients in the control group received volume-matched normal saline in the same schedule. The primary outcome was the incidence of delirium during the first 5 days after surgery. Delirium was assessed with the Confusion Assessment Method (CAM) for non-ventilated patients and CAM for the Intensive Care Unit for ventilated patients.**

Results: **In total, 309 patients who received dexmedetomidine and 310 control patients were included in the intention-to-treat analysis. The incidence of delirium within 5 days of surgery was lower with dexmedetomidine treatment: 5·5 per cent (17 of 309) *versus* 10·3 per cent (32 of 310) in the control group (relative risk (RR) 0·53, 95 per cent c.i. 0·30 to 0·94; $P = 0·026$). The overall incidence of complications at 30 days was also lower after dexmedetomidine (19·4 per cent (60 of 309) *versus* 26·1 per cent (81 of 310) for controls; RR 0·74, 0·55 to 0·99, $P = 0·047$).**

Conclusion: **Intraoperative dexmedetomidine halved the risk of delirium in the elderly after major non-cardiac surgery. Registration number: ChiCTR-IPR-15007654 (www.chictr.org.cn).**

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Introduction

Delirium is a common complication after major surgery, with a reported incidence of up to 54·4 per cent in the elderly[1–4], and up to 91 per cent in the critically ill[5]. The development of delirium is associated with worse early and long-term outcomes[2,5]. The aetiology of postoperative delirium is multifactorial and includes several perioperative factors. For example, deep anaesthesia increases the risk, whereas avoiding deep anaesthesia, with Bispectral Index (BIS) monitoring, decreases anaesthetic consumption and development of delirium[6,7]. Surgery inevitably provokes a stress response including inflammation and cortisol hypersecretion[8], both of which are thought to contribute to the pathogenesis of delirium[9–11]. Furthermore, severe pain and high-dose opioids are also associated with an increased risk[12,13], whereas strategies that relieve pain and decrease opioid consumption reduce the risk of delirium[14–16].

Dexmedetomidine can be used as an adjuvant in the perioperative setting. When administered during surgery, dexmedetomidine reduces the consumption of opioids and anaesthetics[17,18], and blunts the stress response via reduced levels of serum catecholamines, cortisol and cytokines[19]. Intraoperative dexmedetomidine has been shown to reduce the incidence of delirium in children[20]. However, the data reported in adults are controversial. In two RCTs[21,22],

intraoperative dexmedetomidine slightly reduced the incidence of delirium without statistical significance, possibly due to small sample size. In a recent trial by Deiner and colleagues[23], intraoperative dexmedetomidine infusion did not reduce delirium in elderly patients after major non-cardiac surgery. However, the depth of anaesthesia was not monitored, and anaesthetic (propofol and fentanyl) consumption was similar between groups. Anaesthesia was therefore probably deeper in the dexmedetomidine group, which might have increased the risk of delirium[6,7] and negated its effect. Furthermore, suboptimal methodologies have been employed in previous studies, such as unclear randomization and blinding methods[22], and lack of a loading dose of dexmedetomidine[22,23]. The impact of intraoperative dexmedetomidine on the development of postoperative delirium deserves further study.

The purpose of the present study was to investigate whether dexmedetomidine administered during surgery can decrease the rate of delirium in elderly patients after major non-cardiac surgery.

Methods

This was a randomized double-blind placebo-controlled trial with two parallel arms. The study protocol was approved by the Clinical Research Ethics Committee of Peking University First Hospital (2015-987) and registered with the Chinese Clinical Trial Registry on 1 December 2015 (www.chictr.org.cn; registration number ChiCTR-IPR-15007654) (*Appendices S1* and *S2*, supporting information)[24]. Written informed consent was obtained from all patients or their legal representatives before recruitment was done. The study was conducted at Peking University First Hospital.

Participants and baseline data collection

Potential participants were screened by investigators the day before surgery (or on Friday for those who underwent surgery the following Monday). Inclusion criteria were patients aged 60 years or above, scheduled to undergo elective major non-cardiac surgery under general anaesthesia with an expected duration of 2 h or more. Those who met any of the following criteria were excluded: written informed consent not provided; previous history of schizophrenia, epilepsy or Parkinson's disease; visual, hearing, language or other barrier that impeded communication and assessment of delirium; history of traumatic brain injury or neurosurgery; severe bradycardia (heart rate less than 40 beats per minute), sick sinus syndrome, or atrioventricular block of degree 2 or above without pacemaker; severe hepatic dysfunction (Child–Pugh grade C); or renal failure (requirement for renal replacement therapy).

After obtaining written informed consent, baseline data (including demographic data, surgical diagnosis, co-morbidity, and main results of physical and laboratory findings) were collected. Activities of daily living were assessed with the Barthel Index (score range 0–100, with higher score indicating better function)[25]. Cognitive function was assessed with the Mini-Mental State Examination (MMSE) (score range 0–30, with higher score indicating better function)[26]. Delirium status was assessed with the Confusion Assessment Method (CAM)[27]. Investigators performing preoperative screening, data collection and assessment were trained and qualified before the study.

Randomization

Random numbers were created by an independent statistician using the SAS® statistical package version 9.3 (SAS Institute, Cary, North Carolina, USA) in a 1 : 1 ratio with a block size of 4. The results of randomization were sealed in sequentially numbered opaque envelopes and kept by a study coordinator who was not involved in patient recruitment, data collection, perioperative care or postoperative follow-up. During the study, drugs were prepared by the coordinator according to the randomization results, and were provided to the anaesthetists taking care of the recruited patients. In this way, patients were randomized to receive either dexmedetomidine or placebo.

The study drugs, either 200 μg (2 ml) dexmedetomidine (Jiangsu Hengrui Medicine, Jiangsu, China) or 2 ml normal saline, were diluted into 50 ml with normal saline (to a final concentration of 4 μg/ml for dexmedetomidine). All study drugs were colourless, and provided in syringes of the same size and brand. Information regarding randomization, study drug preparation and group allocation was concealed from patients, investigators who performed data collection and postoperative follow-up and anaesthetists, as well as from other healthcare personnel taking care of patients. Blinding was maintained throughout the study.

To ensure patient safety, the group allocation could be unblinded if severe adverse events or any unexpected deterioration in the patient's clinical status occurred. These situations were documented in the case report forms. Unblinded patients were included in the intention-to-treat population, but excluded from the per-protocol analysis.

Intervention, anaesthesia and perioperative care

For patients in the intervention group, a 0·15-ml/kg loading dose of dexmedetomidine (0·6 μg/kg) was administered over a 10 min period before induction of anaesthesia,

followed by a continuous infusion at a rate of 0·125 ml per kg per h (0·5 μg per kg per h) until 1 h before the end of surgery. For patients in the control group, volume-matched normal saline was administered at the same rate, for the same duration. Study drug infusion was performed with an injection pump specially designed for dexmedetomidine administration (Slgo® CP1000; Beijing Slgo Medical Technology, Beijing, China).

The study drug infusion was slowed down or stopped by the anaesthetist if there was severe bradycardia or hypotension that did not improve after routine treatment, new-onset atrioventricular block that did not improve after routine treatment, or any condition that the anaesthetist considered necessary. Reasons for changing the infusion rate were recorded. These patients were included in the intention-to-treat analysis, but excluded from the per-protocol analysis.

Anaesthesia was induced with intravenous propofol and sufentanil, and maintained with intravenous propofol and sufentanil, as well as inhalation of a 1 : 1 nitrous oxide : oxygen mixture. The target anaesthesia depth was to maintain a BIS value between 40 and 60. Rocuronium and/or cisatracurium were administered for muscle relaxation. Fluid infusion and blood transfusion were performed according to routine practice. Blood pressure was maintained within 20 per cent of baseline. Nasopharyngeal temperature was maintained between 36·0 and 37·0°C.

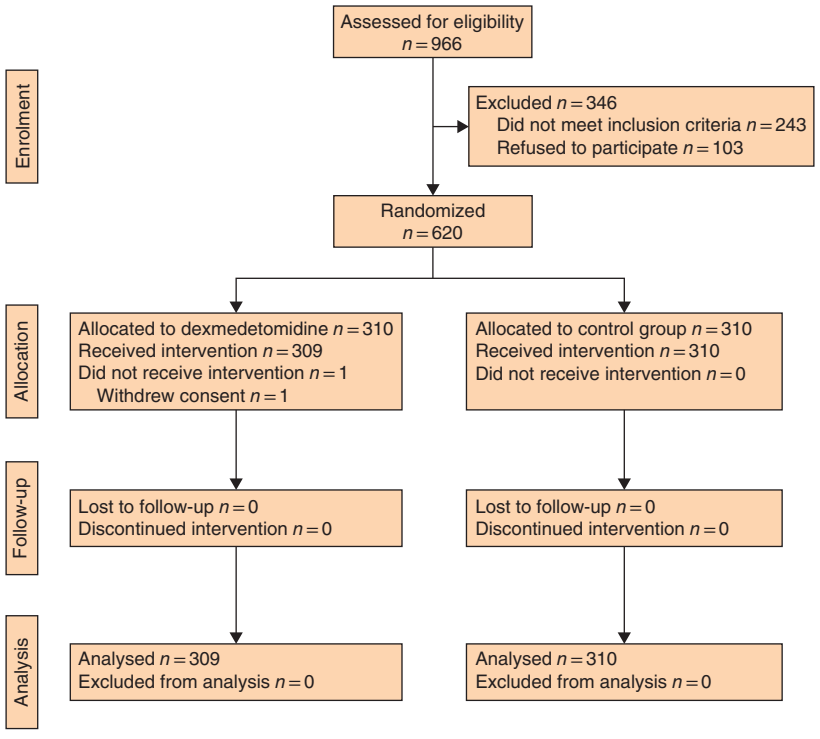
All patients were transferred to the postanaesthesia care unit (PACU) or the ICU before being sent back to a general ward. Patient-controlled intravenous analgesia (PCIA) was provided for postoperative analgesia, which was established with morphine 0·5 mg/ml programmed to deliver a background infusion rate of 0·5 mg/h, and a 1-mg bolus with a lock-out interval of 8 min. For patients with a numerical rating scale pain score (an 11-point scale where 0 indicates no pain and 10 the worst pain) of 4 or greater, supplemental morphine at doses from 2 to 4 mg could be administered at 10-min intervals. Intravenous non-steroidal anti-inflammatory drugs and/or oral tramadol could also be administered.

Outcome assessment

Primary endpoint

The primary outcome was the incidence of delirium during the first 5 days after surgery. Delirium was assessed

Fig. 1 CONSORT diagram for the study



twice daily (at 08·00–09·00 and 19·00–20·00 hours) with the CAM for non-ventilated patients or the CAM for the Intensive Care Unit (CAM-ICU) for ventilated patients[27,28], both of which had been used previously by the authors[9,11,21]. For patients who were discharged or died within 5 days of surgery, the findings of the last delirium assessment were considered as the results of any missing data.

Investigators who did the delirium assessment and postoperative follow-up were trained by psychiatrists before the study started. The training process was repeated at 4- or 6-month intervals during the study. The training programme consisted of the following: a lecture introducing symptoms, diagnosis and treatment of delirium by a psychiatrist; a lecture on how to use the CAM and CAM-ICU; and simulation training courses with patient-actors until the diagnosis of delirium reached 100 per cent consensus with the psychiatrist.

Secondary endpoints

Postoperative pain scores and cumulative morphine consumption were recorded at 24, 48 and 72 h after surgery. Subjective sleep quality was assessed with a numerical rating scale (0 indicates the worst and 10 the best possible sleep) at 08·00–09·00 hours on the first, second and third mornings after surgery[9,11,21]. Other secondary endpoints included the need for ICU admission after surgery, durations of ICU and hospital stay, MMSE score on day 5 after surgery, total non-delirium complications within 30 days, and all-cause 30-day mortality. Non-delirium complications were generally defined as new-onset medical conditions other than delirium that were harmful to recovery and required therapeutic intervention within 30 days of surgery[9,11,21].

Safety outcomes

Adverse events were monitored from the start of study drug administration until 2 h after surgery. Bradycardia was defined as a heart rate lower than 40 beats per minute, and tachycardia as a heart rate of more than 100 beats per minute. Hypotension was defined as a systolic blood pressure of less than 90 mmHg or a decrease of more than 30 per cent from baseline. Hypertension was defined as a systolic blood pressure of more than 180 mmHg or an increase of more than 30 per cent from baseline. Delayed extubation was defined as time to extubation exceeding 2 h from the end of surgery in patients sent to the PACU or 4 h for those in the ICU[29]. Emergence agitation was defined as a Richmond Agitation–Sedation Scale (RASS) score of more than +2 within 30 min of extubation[30]. Oversedation was defined as a RASS score of less than −2 at any time within 2 h after extubation. Desaturation was defined as pulse oxygen saturation of less than 90 per cent. Early postoperative nausea and vomiting (PONV) were defined as those that occurred within 2 h of surgery.

Table 1 Baseline data

	Dexmedetomidine group ($n = 309$)	Control group ($n = 310$)
Age (years)*	69·0(6·6)	69·0(6·4)
Height (cm)*	165·6(7·8)	166·0(7·5)
Bodyweight (kg)*	66·2(10·6)	66·8(11·3)
Sex ratio (F : M)	183 : 126	190 : 120
Preoperative co-morbidity		
Hypertension	148 (47·9)	144 (46·5)
Diabetes	70 (22·7)	62 (20·0)
Coronary artery disease	43 (13·9)	49 (15·8)
Previous stroke	27 (8·7)	33 (10·6)
Arrhythmia	24 (7·8)	31 (10·0)
Congestive heart failure	0 (0)	2 (0·6)
COPD	4 (1·3)	5 (1·6)
Asthma	1 (0·3)	2 (0·6)
Pulmonary embolism	0 (0)	1 (0·3)
Interstitial lung disease	1 (0·3)	1 (0·3)
Hyperlipidaemia	8 (2·6)	13 (4·2)
ASA fitness grade		
I	36 (11·7)	41 (13·2)
II	245 (79·3)	232 (74·8)
III	28 (9·1)	37 (11·9)
CCI score†‡	4 (4–5)	4 (4–5)
MMSE score*§	27·4(2·6)	27·4(2·7)
Barthel Index score*¶	99·9(0·6)	99·9(1·2)
Delirium	0 (0)	0 (0)

Values in parentheses are percentages unless indicated otherwise; values are *mean(s.d.) and †median (i.q.r.). ‡Score ranges from 0 to 37, with higher score indicating worse prognosis. §Score ranges from 0 to 30, with higher score indicating better function. ¶Score ranges from 0 to 100, with higher score indicating better function. COPD, chronic obstructive pulmonary disease; CCI, Charlson Co-morbidity Index; MMSE, Mini-Mental State Examination.

Statistical analysis

Sample size calculation

The rate of delirium has been shown previously[9] to be 14·8 per cent in elderly patients after non-cardiac surgery. A previous study[22] reported that intraoperative dexmedetomidine reduced the incidence of delirium by approximately 60 per cent. The hypothesis was that the incidence of postoperative delirium would be reduced by 50 per cent in the dexmedetomidine group (from 14·8 to 7·4 per cent). With the power set at 80 per cent and a two-sided significance level at 0·05, 564 patients were required to detect a difference. Considering a loss to follow-up rate of

Table 2 Intraoperative and postoperative data

	Dexmedetomidine group (*n* = 309)	Control group (*n* = 310)	*P*§§
Duration of anaesthesia (h)*	4·8(1·8)	4·9(2·0)	0·422¶¶
Intraoperative drugs			
Study drug (ml)†	29·0 (23·0–38·0)	30·0 (23·0–38·0)	0·843##
Propofol (mg)†	810 (600–1100)	957 (669–1320)	< 0·001##
Sufentanil (μg)†	72·0 (55·0–93·0)	78·5 (59·0–106·0)	0·008##
Use of tropisetron	274 (88·7)	266 (85·8)	0·500
Use of NSAIDs‡	12 (3·9)	10 (3·2)	0·659
Use of glucocorticoids	303 (98·1)	301 (97·1)	0·437
Low-dose glucocorticoids§	300 (97·1)	299 (96·5)	0·655
High-dose methylprednisolone¶	3 (1·0)	2 (0·6)	0·686
BIS value*#	50·8(6·5) (*n* = 297)	50·6(6·1) (*n* = 298)	0·586¶¶
> 60% of BIS†	11·0 (4·7–21·3)	18·5 (8·0–38·8)	< 0·001##
40–60% of BIS†	71·0 (58·0–79·9)	69·5 (54·6–81·7)	0·519##
< 40% of BIS†	11·8 (3·4–23·5)	3·7 (0·4–11·6)	< 0·001##
SBP (mmHg)*	127·9(12·1)	128·1(12·9)	0·824¶¶
Duration of surgery (h)*	3·6(1·8)	3·6(1·8)	0·177¶¶
Location of surgery			0·126
Intrathoracic	56 (18·1)	53 (17·1)	
Intra-abdominal	204 (66·0)	224 (72·3)	
Spinal	49 (15·9)	33 (10·6)	
Type of surgery			0·139
Thoracolaparoscopic	234 (75·7)	250 (80·6)	
Open thoracoabdominal/spinal	75 (24·3)	60 (19·4)	
Total fluid infusion (ml)†	2280 (1700–3100)	2250 (1800–3350)	0·968##
Artificial colloid**	127 (41·1)	183 (59·0)	0·183
Allogeneic red blood cells	20 (6·5)	24 (7·7)	0·539
Urine output (ml)†	600 (300–900)	400 (250–700)	< 0·001##
Estimated blood loss (ml)†	100 (50–300)	100 (50–300)	0·606##
PCIA morphine (mg)†	50·0 (40·5–50·0)	49·3 (40·5–50·0)	0·483##
Sedatives within 5 days			
Midazolam	7 (2·3)	12 (3·9)	0·247
Dexmedetomidine	7 (2·3)	9 (2·9)	0·617
Propofol	1 (0·3)	0 (0)	0·499
Analgesics within 5 days			
NSAIDs††	128 (41·4)	136 (43·9)	0·538
Oral tramadol	6 (1·9)	6 (1·9)	> 0·99
High-dose methylprednisolone‡‡	31 (10·0)	21 (6·8)	0·144

Values in parentheses are percentages unless indicated otherwise; values are *mean(s.d.) and †median (i.q.r.). ‡Included parecoxib (40 mg) or flurbiprofen axetil (50 mg), administered before the end of surgery. §Dexamethasone (5–10 mg) or methylprednisolone (40 mg) for prevention of postoperative nausea and vomiting. ¶Methylprednisolone (500–1000 mg) administered during spinal surgery. #Monitored by Bispectral Index (BIS) with data collected at 1-min intervals from end of anaesthesia induction to end of surgery. **Included hydroxyethyl starch and/or succinylated gelatin. ††Included parecoxib (40 mg) or flurbiprofen axetil (50 mg), administered within 5 days of surgery. ‡‡Administered within 5 days in patients after spinal surgery. NSAID, non-steroidal anti-inflammatory drug; BIS, Bispectral Index; SBP, systolic blood pressure; PCIA, patient-controlled intravenous analgesia. §§χ^2 test, except ¶¶independent-samples *t* test and ##independent-samples Mann–Whitney *U* test.

approximately 10 per cent, 620 patients were to be enrolled in the study.

Outcome analysis

Continuous data with a normal distribution were compared using an independent-samples *t* test, and continuous data with a non-normal distribution an independent-samples Mann–Whitney *U* test. Categorical data were compared using the χ^2 test, or continuity correction χ^2 test. Time-to-event data were analysed with Kaplan–Meier survival analysis, with differences between groups assessed by the log rank test. Estimated effect size was reported in

Table 3 Effectiveness outcomes

	Dexmedetomidine group (*n* = 309)	Control group (*n* = 310)	Estimated difference#	*P*‡‡‡
Primary outcome				
Incidence of delirium within 5 days	17 (5·5)	32 (10·3)	0·53 (0·30, 0·94)§§	0·026
Secondary outcomes				
ICU admission after surgery	39 (12·6)	52 (16·8)	0·75 (0·51, 1·11)§§	0·145
With endotracheal intubation	28 (9·1)	25 (8·1)	1·12 (0·67, 1·88)§§	0·658
Length of ICU stay (h)*	21·0 (2·9, 39·0)	20·0 (17·7, 22·2)	0·93 (0·60, 1·43)##	0·734¶¶¶
MMSE score on POD 5†**	27·2(2·7)	27·2(2·3)	−0·1 (−0·5, 0·4)***	0·753§§§
Duration of hospital stay after surgery (days)‡	10·0 (9·1, 10·8)	10·3 (9·3, 11·4)	1·05 (0·90, 1·23)##	0·538¶¶¶
Non-delirium complication††	60 (19·4)	81 (26·1)	0·74 (0·55, 0·99)§§	0·047
Time to onset (days)‡	24·7 (23·5, 25·9)	22·9 (21·5, 24·2)	0·73 (0·51, 0·99)##	0·049¶¶¶
No. of complication events				0·018
0	249 (80·6)	229 (73·9)		
1	57 (18·4)	68 (21·9)		
≥ 2	3 (1·0)	13 (4·2)		
30-day mortality after surgery	0 (0·0)	1 (0·3)	1·00 (0·86, 1·18)##	0·968###
Other predefined outcomes				
NRS score for postoperative pain at rest§‡‡				
At 24 h	1 (1–2)	1 (1–2)	0 (0–0)†††	0·654¶¶¶
At 48 h	1 (0–1)	1 (0–1)	0 (0–0)†††	0·208¶¶¶
At 72 h	0 (0–1)	0 (0–1)	0 (0–0)†††	0·328¶¶¶
NRS score for postoperative pain with movement§‡‡				
At 24 h	4 (3–5)	4 (3–5)	0 (0–0)†††	0·843¶¶¶
At 48 h	3 (2–4)	3 (2–4)	0 (0–0)†††	0·650¶¶¶
At 72 h	2 (1–3)	2 (1–3)	0 (0–0)†††	0·862¶¶¶
NRS score for subjective sleep quality after surgery§¶¶				
1st morning	5 (3–7)	6 (4–8)	−1 (−1–0)†††	0·058¶¶¶
2nd morning	8 (6–8)	8 (7–9)	0 (0–0)†††	0·097¶¶¶
3rd morning	8 (7–9)	9 (8–9)	0 (0–0)†††	0·141¶¶¶

Values in parentheses are percentages unless indicated otherwise; values are *median (95 per cent c.i.), †mean(s.d.), ‡mean (95 per cent c.i.), §median (i.q.r.) and #95 per cent c.i. in parentheses. **Score ranges from 0 to 30, with higher score indicating better function. ††Defined as new-onset medical condition with unfavourable impact on patient recovery and requiring therapeutic intervention within 30 days of surgery; individual non-delirium complications are listed in *Table S1* (supporting information). ‡‡An 11-point scale where 0 indicates no pain and 10 the most severe pain. ¶¶An 11-point scale where 0 indicates worst sleep and 10 best sleep. §§Relative risk; ##hazard ratio; ***mean difference; †††median difference. MMSE, Mini-Mental State Examination; POD, postoperative day; NRS, numerical rating scale. ‡‡‡χ^2 test, except §§§independent-samples *t* test, ¶¶¶ independent-samples Mann–Whitney *U* test and ###log rank test.

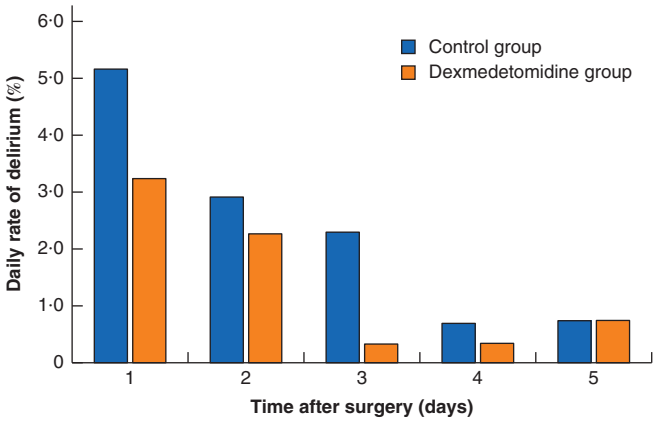
the form of relative risk (RR) or odds ratio (OR) for binary outcomes, hazard ratio (HR) for time to event data, and mean or median difference for continuous data, with 95 per cent confidence intervals. The difference (and 95 per cent c.i.) between two medians was calculated with the Hodges–Lehmann estimator.

Outcome analysis was performed on the intention-to-treat population. For the primary endpoint, per-protocol analysis[24] (*Appendices S1* and *S2*, supporting information) was also performed. Statistical analyses were done with SPSS® version 14.0 (IBM, Armonk, New York, USA) and SAS® version 9.3 (SAS Institute, Cary, North Carolina, USA). All tests were two-tailed, and a two-sided $P < 0{\cdot}050$ was considered statistically significant.

Results

From 2 December 2015 to 27 March 2018, 966 patients were screened for eligibility. Of those, 723 patients were eligible and 620 were enrolled and randomized (*Fig. 1*). During the study, one patient in the dexmedetomidine group withdrew consent and did not receive the study drug, 22 patients had the study drug infusion modified (13 in the dexmedetomidine group and 9 in the control group), 79 patients were discharged from hospital within 5 days of surgery (40 in the dexmedetomidine group and 39 in the control group), and one patient in the control group died on postoperative day 28. No assessment of delirium was terminated because of deep sedation or coma,

Fig. 2 Daily rate of postoperative delirium



No. at risk					
Control	310	309	305	289	271
Dexmedetomidine	309	309	304	293	269

and no emergency unblinding was needed. In the final intention-to-treat analysis, 619 patients were included. The last patient follow-up was performed on 28 April 2018.

Baseline data were well matched between the two groups (*Table 1*). During surgery, propofol and sufentanil consumption was less in patients receiving dexmedetomidine than in those receiving placebo ($P < 0{\cdot}001$ and $P = 0{\cdot}008$ respectively), whereas the mean BIS value was similar between the two groups ($P = 0{\cdot}586$). Urine output was greater after dexmedetomidine infusion ($P < 0{\cdot}001$). Other intraoperative and postoperative variables were comparable between the two groups (*Table 2*).

Analysis of effectiveness

Postoperative delirium developed within 5 days in 17 (5·5 per cent) of the 309 patients who received dexmedetomidine, and in 32 (10·3 per cent) of the 310 patients in the control group (RR 0·53, 95 per cent c.i. 0·30 to 0·94; $P = 0{\cdot}026$) (*Table 3* and *Fig. 2*). Per-protocol analysis also showed a lower rate of delirium in patients who received dexmedetomidine than in the control group: 16 (5·4 per cent) of 296 *versus* 31 (10·3 per cent) of 301 respectively; RR 0·54, 0·30 to 0·97, $P = 0{\cdot}026$).

The rate of non-delirium complications was lower after dexmedetomidine infusion (19·4 per cent *versus* 26·1 per cent in the control group; RR 0·74, 95 per cent c.i. 0·55 to 0·99, $P = 0{\cdot}047$) (*Table 3*). In exploratory analyses, patients who received dexmedetomidine had a lower incidence of surgery-related complications (including gastrointestinal haemorrhage, ileus, anastomotic leak, surgical-site infection and sepsis): seven (2·3 per cent) of 309 *versus* 20 (6·5 per cent) of 310 in the control group (RR 0·35, 0·15 to 0·82; $P = 0{\cdot}011$). Other outcomes including ICU admission after surgery, duration of postoperative ICU and hospital stay, and 30-day mortality did not differ between the groups (*Table 3* and *Table S1*, supporting information).

Safety analysis

The rates of acute agitation ($P = 0{\cdot}007$), tachycardia ($P = 0{\cdot}038$) and PONV within 2 h ($P = 0{\cdot}021$) were lower after dexmedetomidine infusion than in the control group. However, the rates of bradycardia ($P = 0{\cdot}014$) and bradycardia with treatment ($P = 0{\cdot}013$) were higher after dexmedetomidine infusion. The rate of other adverse events did not differ between groups (*Table S2*, supporting information).

Discussion

This study found that, in the elderly undergoing non-cardiac major surgery, intraoperative dexmedetomidine reduced the rate of postoperative delirium. Dexmedetomidine was also associated with a lower rate of acute agitation, perioperative tachycardia, early PONV and 30-day non-delirium complications after surgery.

Postoperative delirium developed in 10·3 per cent of patients who did not receive dexmedetomidine. This was in line with previous studies[15,21,23], but slightly lower than previously reported rates that were used to calculate the

sample size (14·8 per cent)[9]. There are a number of possible reasons for this. First, the patient populations differed. For example, unlike the previous study[9], more patients (such as those with a history of intracranial surgery, severe bradycardia and atrioventricular block) were excluded in the present study, which might have decreased the incidence of delirium[1,16,31]. Second, surgical technique and perioperative management have improved over time; fewer patients in the present study received benzodiazepines and more had thoracolaparoscopic surgery compared with those in the previous study[9]. This might also have decreased the rate of delirium[32,33].

Although a recent trial[34] reported that electroencephalography-guided anaesthetic management did not reduce postoperative delirium compared with usual care in the elderly, the potentially harmful effect of deep anaesthesia on the development of delirium cannot be excluded[35]. Finally, the timing and dose of dexmedetomidine also affected the outcome. In a recent study[36], a loading dose of dexmedetomidine (1 μg/kg over 10 min) administered at induction of anaesthesia (and followed by an infusion of 0·2–0·7 μg per kg per h) was more effective at relieving the stress response and decreasing delirium than dexmedetomidine administered just before the end of surgery. The lack of a loading dose might have reduced the efficacy of dexmedetomidine in preventing delirium in some previous studies[22,23].

The strengths of the present study include the larger sample size than in previous studies[21–23,36], anaesthesia guided by BIS monitoring, and a loading dose of dexmedetomidine as well as a maintenance infusion. The mechanisms of the delirium-sparing effect produced by intraoperative dexmedetomidine are unknown, but it may be associated with the reduced consumption of general anaesthetic during surgery. Preclinical studies have demonstrated the potentially neurotoxic effects of general anaesthetics, including propofol[37]. Dexmedetomidine may attenuate the stress response provoked by surgery in the form of hypersecretion of cortisol and hyperinflammation[18], both of which are associated with an increased risk of delirium[9–11].

In line with previous reports[20,22,38], the results of the present study confirmed that intraoperative dexmedetomidine decreased tachycardia, acute agitation and early PONV. Furthermore, these patients had fewer non-delirium complications, in particular those related to surgery. This may also be related to the attenuated cortisol hypersecretion and hyperinflammation, thereby decreasing gastrointestinal bleeding and preserving immune function, thus reducing infection[18,39–42]. There was a trend towards reduced acute kidney injury (diagnosed according to KDIGO criteria[43]), although it was not statistically significant. This is consistent with previously reported renoprotective effects provided by dexmedetomidine[44], but requires further study. With regard to safety, dexmedetomidine increased the risk of bradycardia, but did not improve postoperative analgesia, possibly due to early interruption of dexmedetomidine infusion 1 h before the end of surgery.

This study has several limitations. First, as a single-centre study, the generalizability of the results may be limited. Second, the haemodynamic effects of dexmedetomidine (such as bradycardia) may weaken the blinding to anaesthetists. The following measures were adopted to avoid the resulting bias during the study: the anaesthetists taking care of patients did not participate in patient recruitment and postoperative follow-up; the investigators who were responsible for postoperative follow-up did not participate in anaesthesia and perioperative care; and the anaesthetists and investigators did not communicate with one another regarding patient information. Finally, although the mean BIS value was well matched between the groups, the percentage of patients with a BIS value above 60 was lower and the percentage with a BIS value below 40 was higher in the dexmedetomidine group.

In elderly patients undergoing major non-cardiac surgery under general anaesthesia, intraoperative administration of dexmedetomidine reduces the incidence of delirium within the first 5 days after surgery. The effect of intraoperative dexmedetomidine on long-term outcome deserves further study.

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Individual deidentified participant data (including primary and secondary outcomes) will be shared on reasonable request after publication of the manuscript. Please contact the corresponding author for relevant data.

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.