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Original Article

The effect of peri-operative dexmedetomidine on the incidence of postoperative delirium in cardiac and non-cardiac surgical patients: a randomised, double-blind placebo-controlled trial

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Summary

Delirium occurs commonly following major non-cardiac and cardiac surgery and is associated with: postoperative mortality; postoperative neurocognitive dysfunction; increased length of hospital stay; and major postoperative complications and morbidity. The aim of this study was to investigate the effect of peri-operative administration of dexmedetomidine on the incidence of postoperative delirium in non-cardiac and cardiac surgical patients. In this randomised, double-blind placebo-controlled trial we included 63 patients aged ≥ 60 years undergoing major open abdominal surgery or coronary artery bypass graft surgery with cardiopulmonary bypass. The primary outcome was the incidence of postoperative delirium, as screened for with the Confusion Assessment Method. Delirium assessment was performed twice daily until postoperative day 5, at the time of discharge from hospital or until postoperative day 14. We found that dexmedetomidine was associated with a reduced incidence of postoperative delirium within the first 5 postoperative days, 43.8% vs. 17.9%, p = 0.038. Severity of delirium, screened with the Intensive Care Delirium Screening Checklist, was comparable in both groups, with a mean maximum score of 1.54 vs. 1.68, p = 0.767. No patients in the dexmedetomidine group died while five (15.6%) patients in the placebo group died, p = 0.029. For patients aged ≥ 60 years undergoing major cardiac or non-cardiac surgery, we conclude that the peri-operative administration of dexmedetomidine is associated with a lower incidence of postoperative delirium.

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Introduction

Delirium is a common postoperative complication, especially in older patients, and is an independent predictor for postoperative mortality. It may put patients at risk of postoperative cognitive dysfunction (POCD) [1], and approximately 25% of patients will develop impaired cognitive function comparable with mild Alzheimer's disease. Conversion rates to dementia up to 70% have been demonstrated in patients who are aged ≥ 65 y [2–4]. For coronary artery bypass grafting and major open abdominal surgery, the incidence of postoperative delirium ranges from 37% to 52% and 5% to 51%, respectively [5]. Delirium

in surgical patients is associated with: increased mortality; prolonged hospital stay; and major peri-operative complications and morbidity [6–8]. For every day of postoperative delirium on the ICU, 1-year survival probability decreases by approximately 10% [9].

Dexmedetomidine is a highly potent α2-agonist, which is used widely in critical care for delirium symptom control. It is known for its sparing properties on delirogenic medication such as sedatives and opioids [10]. Furthermore, it displays antisympathetic, co-analgesic, anxiolytic and sedative effects with minimal respiratory depression. These effects are likely mediated by two mechanisms: first, through the inhibition of tumour necrosis factor production and the inhibitive effects on almost all parts of the brain; and second, through the inhibitive effects of dexmedetomidine on the nucleus coeruleus [11, 12]. In an experimental model in rats, a preventive effect of dexmedetomidine on neuro-inflammation after systemically induced inflammation was shown [13]. Although studies so far have shown conflicting results, recent meta-analyses show a significantly lower incidence of delirium for dexmedetomidine in cardiac and non-cardiac surgical patients, when given intra- and postoperatively [14–17]. Peng et al. also found a significant reduction in 30-day mortality and ICU and hospital stay in cardiac surgical patients [18]. We hypothesise that peri-operative administration of dexmedetomidine significantly reduces the incidence of postoperative delirium in these patients. To our knowledge, this is the first randomised controlled trial investigating the effects of the intra- and postoperative administration of dexmedetomidine in cardiac and non-cardiac surgical patients aged ≥ 60 y.

Methods

This prospective, randomised, double-blind placebo-controlled multicentre trial was conducted from July 2014 to July 2018 at the Department of Anaesthesia and Intensive Care Medicine, Charité – Universitätsmedizin Berlin. Stratified randomisation took place in four groups according to the type of surgery (cardiac or major open abdominal) and whether the patient received beta-blocker therapy or not. All patients provided oral and written informed consent.

Patients aged ≥ 60 y undergoing either major elective cardiac (coronary artery bypass graft surgery with a left ventricular ejection fraction of > 30%) or major open abdominal (pancreatic, hepatic, gastric or intestinal) surgery at our centre were assessed for eligibility. All patients were to undergo general anaesthesia and receive postoperative analgesia according to the German S3-guideline on analgesia, sedation and delirium management in intensive care medicine [19]. Propofol was used for induction of anaesthesia and some patients were premedicated with midazolam at the discretion of the anaesthetist. General exclusion criteria were: valvular surgery; off-pump cardiac surgery; known drug intolerance or allergy to dexmedetomidine; accommodation in an institution due to an official or judicial order; employees of the institution; those unable to provide written consent; patients with no fixed abode; patients participating in other medical studies; patients previously diagnosed or suspected to suffer from major neurocognitive disorder, defined by a mini-mental state examination (MMSE) score < 24; severe audiovisual impairment; traumatic brain injury; intracranial bleeding < 1 y before the inclusion date; psychiatric illness; history of alcohol or drug abuse; pregnancy; haemodynamic dysfunction (severe hypotension, defined as a mean arterial pressure < 55 mmHg despite optimal preload and vasopressor therapy); second- or third-degree atrioventricular heart block; severe sinus bradycardia (< 50 bpm at rest); spinal injury with autonomic dysfunction; pre-operative cerebrovascular accident with residual neurological deficit; Child C liver cirrhosis; intra-operative use of remifentanil or clonidine; additional administration of dexmedetomidine within 3 months after inclusion; and planned postoperative deep sedation below a Richmond Agitation Sedation Scale (RASS) of −4.

Dosing of study medication was calculated according to adjusted body weight. Intra-operatively, patients received either a fixed rate of dexmedetomidine 0.7 $\mu g.kg^{-1}.h^{-1}$ or an equivalent volume of saline, starting 10 min after induction of anaesthesia. If haemodynamic side-effects occurred that could not be mitigated by optimisation of preload or administration of orciprenaline, the rate was reduced to 0.4 $\mu g.kg^{-1}.h^{-1}$ or 0.2 $\mu g.kg^{-1}.h^{-1}$, if necessary. Approximately 30 min before the expected end of surgery, the rate of infusion was set to 0.4 $\mu g.kg^{-1}.h^{-1}$. After tracheal extubation and arrival in ICU, the dose was further reduced by half every 20 min to achieve a RASS of −1 or 0. If oversedation was suspected, the infusion was paused for a maximum of 30 min. If the patient was agitated (RASS > 0), the dose could be increased by 0.2 $\mu g.kg^{-1}.h^{-1}$ stepwise every 20 min up to a maximum of 1.4 $\mu g.kg^{-1}.h^{-1}$. Syringes with either dexmedetomidine or saline were labelled with a code only and provided by the hospital pharmacy, thus blinding investigators, clinicians and the patient.

Syringe label codes were created by the institute for biometrics and clinical epidemiology. In the event of an emergency, the patient could be unblinded by means of an emergency envelope, which was provided for each patient.

Instead of intravenous (i.v.) atropine, i.v. orciprenaline was used to treat bradycardia. General anaesthesia was maintained with i.v. propofol, volatile inhalational anaesthetic agent or both. Standard clinical practices were otherwise maintained. Depth of anaesthesia was closely monitored by means of EEG monitoring (Sedline®, Masimo, Irvine, CA, USA). Anaesthetists were instructed to keep the 'patient state index' above 25 and avoid burst suppression. Data were blinded until the analysis of all patients had been completed and protocol violations were documented.

Once scheduled for surgery, participants were contacted on the inpatient ward or pre-operative screening outpatient clinic one or more days before surgery. Patients were evaluated for study eligibility by a physician before inclusion and were given a unique identifier. Baseline patient characteristics, including pre-operative morbidity and peri-operative risk-factors were assessed from patient notes, standardised questionnaires and during patient interview, and clinical examinations performed by trained research staff according to standard operating procedures. Polypharmacy was defined as the use of more than five drugs.

Primary outcome was the incidence of postoperative delirium, as screened for with the Confusion Assessment Method for the Intensive Care Unit for those on ICU or the Confusion Assessment Method for those on the ward, twice daily up to postoperative day 5 and on either discharge or postoperative day 14 at the latest. During treatment on ICU, delirium assessment also included the Intensive Care Delirium Screening Checklist. A structured review of the patient notes was performed to detect possible missed episodes of delirium between screening periods. Duration of delirium was measured by positive delirium screening in days. At all delirium screening time-points, agitation and sedation were assessed with the RASS and pain scored with the NRS or behavioural pain scale (BPS, BPS-NI) in accordance with European Society of Anaesthesiology guidelines on the prevention of postoperative delirium [20]. Peri-operative anxiety levels were assessed with the Faces Anxiety Scale [21].

Neurocognitive testing was performed at baseline before surgery, at hospital discharge and 3 months after surgery. The cognitive test battery included four computerised and two non-computerised tests. Computerised tests included: pattern recognition memory; spatial recognition memory; spatial span; and choice reaction time. Non-computerised tests included visual verbal learning test and the Stroop-colour-word-interference test. Detailed descriptions of cognitive tests used are provided in online Supporting Information Appendix S1. The MMSE was used to screen for major neurocognitive disorder and dementia at all test time-points. Pre-operative performance of < 24 points resulted in exclusion from the study.

Testing was performed in accordance with a standard operating procedure and plausibility of data was checked by two independent assessors. Imputation of missing cognitive data was only performed if the patient attended cognitive testing at the scheduled time-point, but single values were missing. Missing data were replaced with the worst performance value of the entire patient group if testing was incomplete due to lack of concentration or not understanding the test instruction. When values were missing at random, for example, due to technical difficulties or environmental disturbances, random forest imputation was applied to replace missing values [22]. To adjust for natural variability in cognitive performance and learning effects in repeated cognitive testing, POCD was defined according to the reliable change index with the International Study of Post-Operative Cognitive Dysfunction criteria proposed by Rasmussen [23], which we implemented in an R package.

Peri-operative vital parameters, EEG parameters, blood gas analyses, and any medication given were closely monitored by a physician or study assistant. Blood samples were drawn before and on postoperative day 1. Any adverse events, such as intra-operative bradycardia or hypo-/hypertension were documented and reported to the Federal Institute for Drugs and Medical Devices.

Until the last follow-up visit, data regarding any postoperative organ dysfunction up to 90 days were reported. Postoperative infections were assessed according to surgical site infections and US Centers for Disease Control and Preventions definitions [24]. Severity of illness on ICU was measured by the use of three morbidity scores (SOFA, SAPS 2, and APACHE). Furthermore, 90-day mortality, ICU and hospital length of stay and mechanical ventilation and weaning failure were documented. After 3 months, questionnaires were used to collect data pertaining to sleep; quality of life; anxiety; and pain. On completion of data collection, the investigators performed a detailed plausibility check of the case report forms. Only after approval by the clinical monitor were the forms entered into the database. Then, a plausibility check of the database took place by two investigators. After completion, the study group was unblinded and the database was evaluated by a statistician.

Our sample size calculation was based on an assumed incidence of postoperative delirium of 45% in this population [25]. With intervention, a relevant reduction to a delirium incidence of 10% was predicted [26]. We used nQuery Advisor Release 7.0 (Stat. Solutions Ltd. and South

Bank, Cork, Ireland) to calculate sample size with 80% power and an α error probability of 0.05, yielding a sample size of 58 patients. Including a withdrawal rate of 5%, a total of 62 patients (31 per group) were required. Study results were analysed on an intention-to-treat basis.

All outcomes were analysed with either χ^2-tests (categorical variables) or Wilcoxon-Mann-Whitney tests (continuous variables) depending on scale. As secondary outcomes were analysed exploratively, no adjustment for multiple testing was made. The level of significance was defined in all cases to $\alpha = 5\%$ (two-sided). Statistical analyses were conducted using SPSS 25 and R 3.5.1.

Results

Between July 2014 and July 2018, 484 patients were assessed for eligibility of which 63 (13.0%) were enrolled, and three later withdrew. One withdrew before surgery shortly after providing written informed consent and another was unexpectedly scheduled for emergency surgery, before the originally planned surgery. One cardiac surgical patient withdrew participation postoperatively. Therefore, 60 patients were analysed on an intention-to-treat basis: 28 in the dexmedetomidine group and 32 in the placebo group (Fig. 1; Table 1). In total, 46 (77%) underwent major open abdominal surgery. In the dexmedetomidine group, 22 (79%) underwent abdominal surgery as compared with 24 (75%) in the placebo group, p = 0.744. Of the 60 patients, 36 (60%) were treated in accordance with the study protocol. In the remaining 24, several protocol violations were recorded. Serious protocol violations included: two stratifications in the wrong treatment group; variation in the length of treatment with study medication; and subsequent occurrence of an exclusion criterion or violation of an inclusion criterion. With regard to the occurrence of protocol violations, there was no significant difference between the intervention and placebo groups.

For the primary outcome, the incidence of postoperative delirium was significantly lower in the dexmedetomidine group as compared with placebo (Fig. 2; Table 2). There was no difference in the severity of postoperative delirium between groups and no difference in mean (SD) duration of delirium between the dexmedetomidine and placebo group, 2.00 (1.41) vs. 0.89 (0.94) days respectively, p = 0.149. The median (IQR [range]) baseline MMSE was 29 (28–30 [25–30]) in the dexmedetomidine group and 29 (28–29 [26–30]) in the placebo group. At 90 days postoperative follow-up, there was no difference in MMSE scores as compared with baseline, p = 0.465. Postoperative neurocognitive dysfunction was found in four (13%) patients. No difference in POCD incidence was found between the groups. The incidence of POCD was not influenced by sex, ASA physical status, the occurrence of postoperative delirium or other peri-operative precipitating factors, such as educational status and MMSE score.

Reported anxiety on the first day after surgery was significantly lower in the dexmedetomidine group as compared with placebo. This difference was only present on the first day after surgery and was not detected during postoperative days 2–5 when the study drug was not administered. Overall, 36 (60%) patients displayed a RASS between 0 and -1 at each postoperative visit, showing no difference between the dexmedetomidine and placebo group with 17 (61%) and 19 (59%), respectively, p = 0.916. The other 24 (40%) patients had a RASS lower than -1 in at least one visit. A Glasgow Coma Scale Score of 15 was reached at each visit in 7 (25%) patients in the dexmedetomidine group and 11 (34%) patients in the placebo group, p = 0.429. Although showing no difference between both groups, pain scores were mainly within an acceptable range (NRS $\leq$ 4) during all postoperative visits. The mean (SD) number out of total visits with increased pain (NRS $\geq$ 4) was 1.18 (1.94) in the dexmedetomidine group and 2.16 (2.77) in placebo group, p = 0.068.

Median (IQR [range]) duration of bradycardic episodes, of which there were 36 in total and with no difference in incidence between the groups, was 90 (22–90 [10–1200]) min in the dexmedetomidine group and 145 (30–830 [16–1360]) min in the placebo group, p = 0.558. Intra-operative heart rate was less variable in the dexmedetomidine group as compared with placebo group. The differences in heart rate between the two groups were more pronounced the longer the surgery lasted (Fig. 3).

In total, 34 postoperative infections were recorded in the study population with 13 (46%) in the dexmedetomidine group and 21 (66%) in the placebo group, p = 0.134. For the collection of morbidity scores, there were 18 (30%) patients with missing data, because not all of the patients stayed in ICU for at least 1 day. There were no differences between SOFA, SAPS 2 and APACHE scores between the groups. The high recorded severity of illness scores were in accordance with the age of the study population and the type of surgery undertaken.

In the follow-up period of 90 postoperative days, no patients in the dexmedetomidine group and 5 (16%) patients in the placebo group died, p = 0.029 (Fig. 4). No significant difference concerning ICU or hospital length of stay was found between the two groups (Table 2). Quality of life assessment with the EQ-5D questionnaire yielded no statistically significant difference between the two groups. At

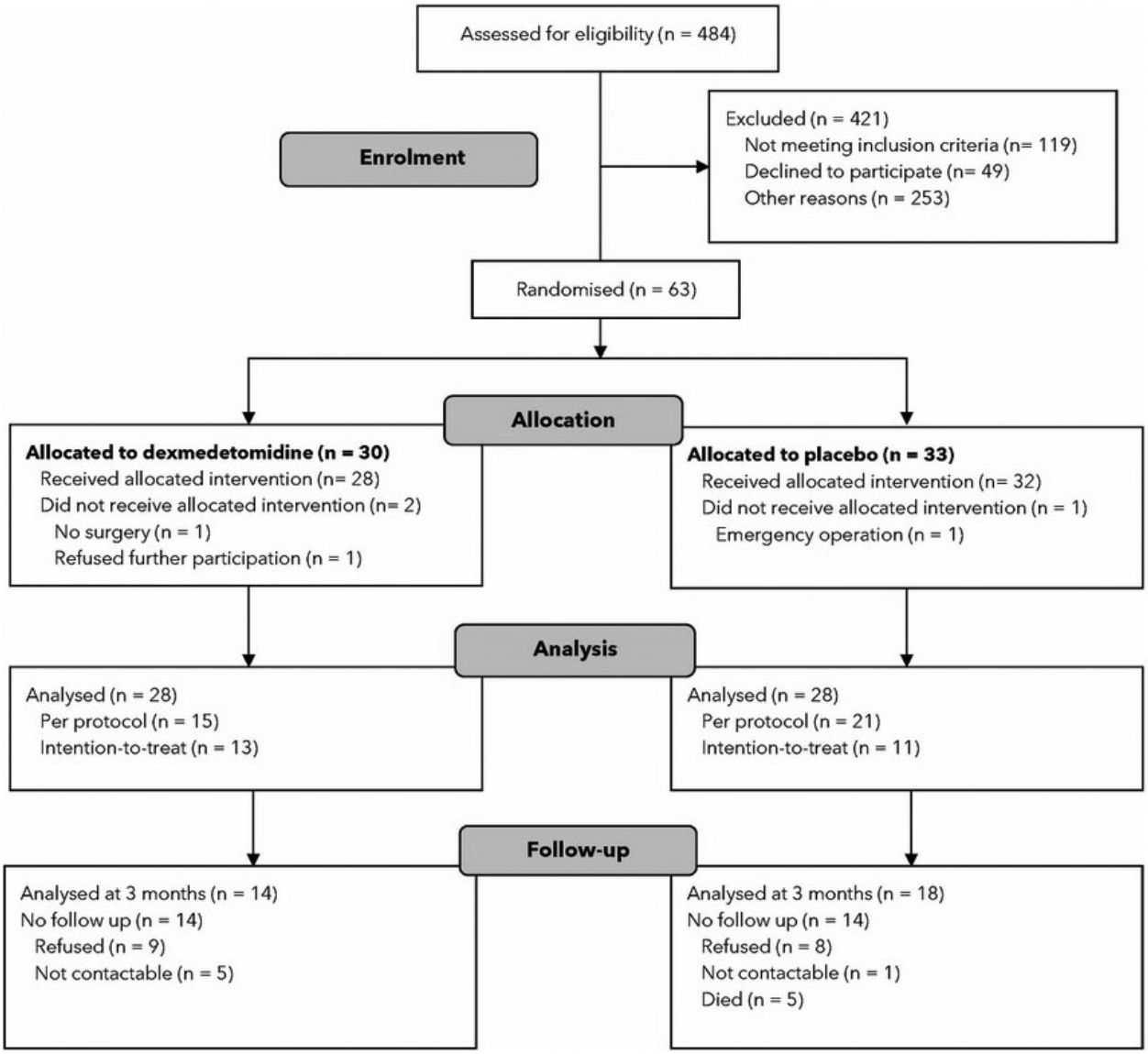

Figure 1 Study flow diagram.

3 postoperative months, there was no significant difference in sleep quality between the groups, p = 0.162, and no severe unexpected serious adverse reactions were observed.

Discussion

For non-cardiac and cardiac surgical patients aged ≥ 60 y undergoing major surgery, we found a significant reduction in postoperative delirium to 18% from 44% when dexmedetomidine was administered in the peri-operative period as compared with placebo. We also found a significant reduction in anxiety on the day of surgery. Intra-operative heart rate was also less variable in the dexmedetomidine group during the course of surgery. During the last hours of surgery, heart rate was lower in the dexmedetomidine group compared with placebo. The differences in heart rate between the groups were more pronounced the longer surgery lasted. This might be related to a reduction in sympathetic tone caused by dexmedetomidine. No difference was found between groups for: severity of delirium; incidence of POCD; postoperative decline of MMSE; and incidence of bradycardia. No difference was found between groups for: sedation scores; incidence of postoperative infections; organ dysfunctions; severity of illness; ICU and hospital length of stay; and quality of life and sleep. We believe that dexmedetomidine is safe for use in the peri-operative

Table 1 Baseline characteristics of 60 included patients randomly allocated to either dexmedetomidine or placebo. Values are mean (SD), number (proportion) or median (IQR [range]).

	Dexmedetomidine n = 28	**Placebo n = 32**
Age; y	70.43 (7.14)	70.5 (6.23)
Female	9 (32%)	9 (28%)
BMI; $kg.m^{-2}$	26.97 (4.93)	28.03 (4.66)
Site of surgery		
Pancreatic surgery	13 (46%)	16 (50%)
Other intra-abdominal procedure	9 (32%)	8 (25%)
Cardiac	6 (21%)	8 (25%)
ASA physical status		
1 or 2	14 (50%)	16 (50%)
3 or 4	14 (50%)	16 (50%)
Receiving daily beta-blocker intake	15 (53%)	18 (56%)
Pre-operative MMSE		
25–27	7 (26%)	6 (19%)
28–30	20 (74%)	26 (81%)
Charlson comorbidity index	3.36 (2.20)	3.25 (2.16)
Underlying malignancy	19 (68%)	21 65.6)
Pre-operative Faces Anxiety Scale score > 1	10 (36%)	12 (38.7)
Polypharmacy	13 (46%)	11 ((34.4)
Pre-operative NYHA		
0	18 (64%)	16 (50%)
1-3	10 (36%)	16 (50%)
Pre-operative heart rate; $beats.min^{-1}$	71.5 (64.5–79.5 [52.0–108.0])	70.5 (63.0–80.0 [54.0–103.0])
Pre-operative plasma haemoglobin; $g.dl^{-1}$	12.2 (11.3–13.2 [7.4–15.4])	13.1 (11.7–13.8 [8.1–15.7])

MMSE, mini-mental state examination; NYHA, New York Heart Association Classification

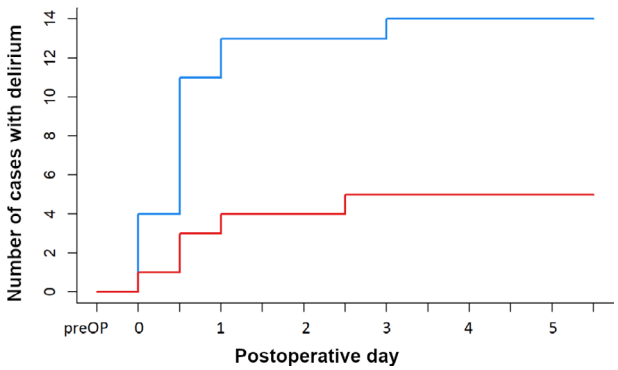

Figure 2 Cumulative case count of delirium in dexmedetomidine (red) and placebo (blue) groups.

period, and the risk-benefit profile of its use did not change during our trial. This is in accordance with latest meta-analysis regarding efficacy and safety of dexmedetomidine administration in cardiac surgery patients [27].

Overall, our results are in accordance with the latest relevant meta-analyses and randomised controlled trials [14–16]. Since these meta-analyses were published, there have been several new studies on the effect of the intra-operative use of dexmedetomidine on the incidence of postoperative delirium [28–30]. In total, there are six non-cardiac and three cardiac randomised controlled trials, and two retrospective observational studies. Deiner et al. report the largest prospective multicentre non-cardiac randomised controlled trial [31]. They included 390 patients

Table 2 Primary and second outcomes of patients randomly allocated to peri-operative dexmedetomidine and placebo. Values are number (proportion), median (IQR [range]) or mean (SD).

	Dexmedetomidine n = 28	**Placebo n = 32**	**p value**
Postoperative delirium	5 (18%)	14 (44%)	0.031
Duration of surgery and anaesthesia; min	434 (254–570 [144–890])	412 (330–525 [161–730])	0.773
Postoperative Faces Anxiety Scale score > 1	3 (11%)	13 (41%)	0.008
Bradycardic episodes	17 (67%)	19 (59%)	0.916
Maximum noradrenaline dose; $\mu g.kg^{-1}.min^{-1}$	0.07 (0–0.1 [0–0.3])	0.1 (0.1–0.2 [0–1.3])	0.064
Severity of illness			
SOFA	7 (5–9 [3–14])	6 (5–9 [1–10])	0.389
SAPS 2	49 (40–48 [28–69])	40 (33–50 [26–61])	0.104
APACHE	20 (15–24 [7–34])	20 (14–24 [8–29])	0.833
ICU length of stay; days	2.3 (0.8–4.5 [0–21.8])	2.8 (1.0–4.8 [0–29.7])	0.614
Length of hospital stay; days	23.5 (20.3)	21.0 (15.6)	0.807
Return to theatre	14 (50%)	12 (38%)	0.475
Three-month mortality	0	5 (16%)	0.029

FAS, Faces Anxiety Scale; SOFA, sequential organ failure assessment score; SAPS, simplified acute physiology score; APACHE, acute physiological assessment and chronic health evaluation score.

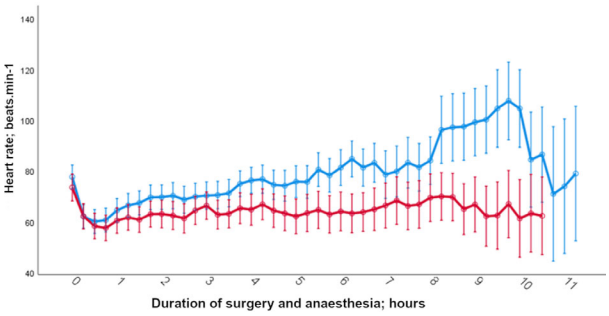

Figure 3 Intra-operative heart rate in dexmedetomidine (red) and placebo (blue) groups. As the duration of surgery increases, the number of patients analysed decreases as demonstrated by the widening of 95%CI bars.

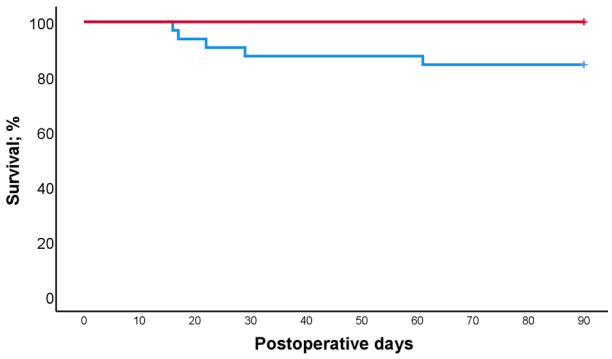

Figure 4 Mortality up to 90 days postoperatively in dexmedetomidine (red) and placebo (blue) groups.

aged ≥ 68 y who were administered 0.5 $\mu g.kg^{-1}.h^{-1}$ dexmedetomidine from the start of the procedure until 2 h postoperatively. They found no significant reduction in the incidence of postoperative delirium, as measured by the Confusion Assessment Method and Confusion Assessment Method for the Intensive Care Unit. However, patients with ASA physical status grades of > 3 or those planned for postoperative admission to ICU were not included, and major surgery was only defined by a stay > 2 days in hospital. Moreover, patients were only assessed for delirium once during their whole hospital stay. This might explain their low recorded incidence of postoperative delirium in both groups, despite having a high baseline incidence of mild cognitive impairment of > 60%. In contrast, our study did not include patients with a MMSE < 24 and focused mainly on duodenum-preserving pancreatic head resection and coronary artery bypass graft surgery with a probable longer postoperative stay in ICU. Furthermore, in our study, dexmedetomidine was administered until a RASS of 0/-1 was achieved, ranging from 165 min to 2945 min. Our focus on patients undergoing major surgery, longer postoperative administration of dexmedetomidine and the slightly higher intra-operative dose of dexmedetomidine could all be reasons for the effect found.

Five smaller non-cardiac randomised controlled trials have been undertaken with participant numbers ranging from 79 to 318: two in orthopaedic surgery; one in maxillofacial surgery; one in thoracic surgery; and one in major abdominal surgical patients. Studies were heterogeneous in timing and dosage of dexmedetomidine.

Dosage ranged from 0.2 $\mu g.kg^{-1}.h^{-1}$ to 0.7 $\mu g.kg^{-1}.h^{-1}$. Among all randomised controlled trials, five used a loading dose between 0.6 and 1.0 $\mu g.kg^{-1}$ [28, 30, 32–34]. Intra-operative timing varied with the beginning of administration ranging from the beginning of anaesthesia to 1 h before the end of surgery. The end of dexmedetomidine administration ranged from 30 min before the end of surgery to the next morning after surgery. One orthopaedic study used dexmedetomidine as an adjunct to regional anaesthesia [30]. All had postoperative delirium as the primary endpoint.

Lee et al. analysed 318 patients aged ≥ 65 y undergoing laparoscopic surgery [32]. Patients were randomly allocated to three groups. One (n = 95) received a dexmedetomidine 1 $\mu g.kg^{-1}$ bolus, followed by 0.2 $\mu g.kg^{-1}.h^{-1}$ to 0.7 $\mu g.kg^{-1}.h^{-1}$ infusion from induction of anaesthesia to the end of surgery. A second group (n = 114) received a dexmedetomidine bolus only. A third control group received saline only (n = 109). They found a significant reduction of the incidence of postoperative delirium of 9.5% in the first group vs. 18.4% and 24.8% in the other two groups, respectively.

Liu et al. [35] analysed 197 orthopaedic surgical patients aged ≥ 65 y. They were subdivided into a group with amnesic mild cognitive impairment (aMCI) (n = 80) and a group without (n = 120). Patients were randomly allocated into four groups: aMCI dexmedetomidine, aMCI control, control dexmedetomidine and saline. Dosage ranged from 0.2 $\mu g.kg^{-1}.h^{-1}$ to 0.4 $\mu g.kg^{-1}.h^{-1}$, which was administered after induction until 20 min before the end of surgery. They found a statistically significant reduction in the incidence of postoperative delirium in both the non-aMCI and aMCI dexmedetomidine groups compared with their respective placebo groups. A randomised controlled trial by Mei et al. analysed 296 patients aged ≥ 65 undergoing hip arthroplasty into groups receiving dexmedetomidine or propofol sedation as an adjunct to regional anaesthesia [30]. Patients in the dexmedetomidine group received a bolus of 0.8–1.0 $\mu g.kg^{-1}$ followed by a continuous rate of 0.1–0.5 $\mu g.kg^{-1}.h^{-1}$. They found a statistically significant reduction in postoperative delirium incidence in the dexmedetomidine group.

Kim et al. conducted a randomised controlled trial, which analysed 120 patients aged ≥ 56 y undergoing thoracoscopic lung resection [29]. Dexmedetomidine was administered at 0.5 $\mu g.kg^{-1}.h^{-1}$ immediately before induction of anaesthesia until the end of surgery. Although finding a reduced incidence for emergence agitation in the dexmedetomidine group, no difference was found for the incidence of postoperative delirium. The randomised controlled trial of Yang et al. analysed 79 patients undergoing maxillofacial surgery. They did not find a difference in the incidence of delirium either [36]. However, administration started relatively late (1 h before end of surgery) and they did not include older elderly patients exclusively.

Two retrospective cohort studies looked at the effects of intra-operative administration of dexmedetomidine and postoperative delirium. Shin et al. performed a retrospective cohort study that included 855 patients aged ≥ 65 y undergoing regional anaesthesia for orthopaedic surgery. Of those, 222 received dexmedetomidine and were compared with a propensity-score-matched sub-group of 263 patients that received propofol sedation [37]. Dexmedetomidine was given with a starting bolus of 1 $\mu g.kg^{-1}$ followed by an infusion of 0.1–0.5 $\mu g.kg^{-1}.h^{-1}$. Primary outcome was abnormal psychomotor behaviour, defined as RASS ≥ 2, or agitated behaviour found by chart review. Shin et al. found a significant reduction in agitated behaviour in those who received dexmedetomidine. However, baseline incidence of agitated behaviour was low (only six patients in the dexmedetomidine and 17 patients in the placebo group) and no delirium detection tool was used. Cheng et al. conducted a retrospective cohort study of 505 patients aged ≥ 65 y who underwent cardiac surgery [38]. Of those, 283 (56.0%) received dexmedetomidine (0.24–0.6 $\mu g.kg^{-1}.h^{-1}$), which was started after cardiopulmonary bypass and until 24 h postoperatively. Patients who received dexmedetomidine had a statistically significant reduction in delirium rate of 7.21% vs. 10.95%. However, no delirium detection tool was used, as delirium was assumed if there were documented illusions, confusion or cerebral excitement.

We identified three relevant randomised controlled trials of cardiac surgical patients who received dexmedetomidine. Li et al. randomised 285 patients aged ≥ 60 y undergoing coronary artery bypass graft and/or valve replacement surgery [33]. They administered dexmedetomidine at a rate of 0.6 $\mu g.kg^{-1}.h^{-1}$ once i.v. access was established for 10 min and then switched to a rate of 0.4 $\mu g.kg^{-1}.h^{-1}$ until the end of surgery. After surgery, a rate of 0.1 $\mu g.kg^{-1}.h^{-1}$ was continued until the end of mechanical ventilation. Although Li et al. did not find a reduction in postoperative delirium, considering the unexpectedly low delirium incidence (4.9% in the dexmedetomidine group vs. 7.7% in the placebo group), they state that their trial may have been underpowered. Massoumi et al. randomly allocated 88 patients undergoing coronary artery bypass graft surgery aged 40–80 y [28].

After receiving a dexmedetomidine subcutaneous loading dose of 1 $\mu g.kg^{-1}$, an infusion rate of 0.2–0.7 $\mu g.kg^{-1}.h^{-1}$ followed. They found a significant reduction in postoperative delirium and delirium severity. However, the way in which delirium and delirium severity was measured was not further defined. Sheikh et al. randomly allocated 60 patients aged 15–60 y [34]. The intervention group received a bolus of dexmedetomidine of 1 $\mu g.kg^{-1}$ over 10 min, followed by infusion at a rate of 0.2–0.6 $\mu g.kg^{-1}.h^{-1}$ after induction of anaesthesia. A significant reduction in postoperative delirium was found. However, in their methods Sheikh et al. do not disclose when the dexmedetomidine infusion was stopped. Additionally, they did not use a delirium detection tool and assumed postoperative delirium when comparatively short course illusions, confusion, and cerebral excitement in the postoperative period were reported.

To the best of our knowledge, this is the first study to evaluate administration of dexmedetomidine intra- and postoperatively. The main limitation of our study was a relatively small sample size. This was the first randomised controlled trial that investigated the preventive effects of intra- and postoperatively administered dexmedetomidine on postoperative delirium in cardiac and non-cardiac surgical patients. There was a focus on elderly high-risk surgery patients with a probable longer stay in ICU, and this patient population is also susceptible to developing delirium. Delirium was assessed twice daily, enabling a more accurate estimate of the incidence of delirium. Moreover, we gathered a multitude of outcomes enabling a broad analysis of delirium and looking at multiple postoperative outcomes. Incidence of POCD in a relatively small sample size was low due to the application of a conservative cut off ($Z \leq -1.96$) to define relevant cognitive change. We could not draw a conclusion concerning the effect of dexmedetomidine on long-term cognitive outcome after surgery.

When carefully selected for age and scope of surgery, intra-operative administration of dexmedetomidine can yield a significant reduction in the frequency of postoperative delirium compared with placebo. Our study found a significant reduction in postoperative delirium from 44% to 18%, which is similar to the results from the latest relevant meta-analyses and randomised studies. Furthermore, there was a significant reduction of postoperative anxiety and no adverse effects were reported. Other cognitive parameters, including POCD, were not found to be statistically significant. Because of our relatively small sample size, future studies are warranted, powered for longer-term outcomes. On the basis of these findings, peri-operative administration of dexmedetomidine seems to be a promising and safe way to effectively reduce postoperative delirium in carefully selected high-risk patients.

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Supporting Information

Additional supporting information may be found online via the journal website.

Appendix S1. Neurocognitive tests used.