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ORIGINAL ARTICLE

Dexmedetomidine for prevention of postoperative delirium in older adults undergoing oesophagectomy with total intravenous anaesthesia

A double-blind, randomised clinical trial

Jun Hu, Mudan Zhu, Zongbin Gao, Shihao Zhao, Xiaomei Feng, Jinbao Chen, Ye Zhang and Mervyn Maze

BACKGROUND Dexmedetomidine is known to be a sedative. Recent studies suggest that administration of dexmedetomidine can prevent postoperative delirium (POD) which has been confirmed as a common complication after major surgery. However, its effects in patients undergoing oesophagectomy are scarce.

OBJECTIVE To investigate the efficacy and safety of dexmedetomidine in reducing POD in elderly patients after transthoracic oesophagectomy with total intravenous anaesthesia (TIVA).

DESIGN A randomised, double-blind, placebo-controlled trial.

SETTING Single-centre, tertiary care hospital, November 2016 to September 2018.

PATIENTS Eligible patients ($n = 177$) undergoing transthoracic oesophagectomy were randomly assigned to receive total intravenous anaesthesia (TIVA, $n = 87$) or dexmedetomidine with TIVA (DEX-TIVA, $n = 90$).

INTERVENTIONS Patients receiving DEX-TIVA received a loading dose of dexmedetomidine (0.4 $\mu g\,kg^{-1}$), over 15 min, followed by a continuous infusion at a rate of 0.1 $\mu g\,kg^{-1}\,h^{-1}$ until 1 h before the end of surgery. Patients receiving TIVA received physiological saline with a similar infusion rate protocol.

OUTCOME MEASURES The primary outcome was the incidence of POD. The secondary endpoints were the incidence of emergence agitation, serum interleukin-6 (IL-6) levels and haemodynamic profile.

RESULTS All randomised patients were included with planned intention-to-treat analyses for POD. Delirium occurred in 15 (16.7%) of 90 cases given dexmedetomidine, and in 32 (36.8%) of 87 cases given saline ($P = 0.0036$). The DEX-TIVA group showed less frequent emergence agitation than the TIVA group (22.1 vs. 48.0%, $P = 0.0058$). The incremental change in surgery-induced IL-6 levels was greater in the TIVA group than DEX-TIVA group ($P < 0.0001$).

CONCLUSION Adding peri-operative dexmedetomidine to a total intravenous anaesthetic safely reduces POD and emergence agitation in elderly patients undergoing open transthoracic oesophagectomy. These benefits were associated with a postoperative reduction in circulating levels of the pro-inflammatory cytokine IL-6 and stabilisation of the haemodynamic profile.

TRIAL REGISTRATION Chinese Clinical Trials Register Identifier: ChiCTR-IPR-17010881.

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Introduction

Postoperative delirium (POD), is a common and life-altering complication with an incidence 10 to 60% in the elderly surgical populations.[1,2] POD is associated with increased mortality and morbidity resulting in longer hospital stays and increased healthcare costs.[3] Peri-operative factors such as bleeding, infection and pain can each

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increase the risk for the development of POD.[4–6] The extensive and traumatic nature of an open oesophagectomy can intensify these risk factors,[7] and require risk-mitigating peri-operative strategies to curtail the development of delirium.

Surgical interventions and invasive procedures can trigger an aseptic surgical inflammatory response in patients.[8] Activation of the innate immune system and the subsequent inflammatory response represents the primary host defence against various peri-operative insults; however, if uncontrolled, the inflammatory response may ultimately be detrimental to the patient.[9]

In considering risk-mitigating strategies, it is important to identify possible targets, which when disabled, could ameliorate the pathogenic process. Following aseptic surgical trauma, high-mobility group box 1 protein is released and interacts with the immune system to upregulate pro-inflammatory cytokines[10–12] that are correlated to development of POD.[13–15] The α2-adrenergic receptor agonist, dexmedetomidine has been shown to decrease pro-inflammatory cytokines by activating the cholinergic anti-inflammatory pathway.[16,17] Furthermore, dexmedetomidine has also been shown to reduce the requirement for sevoflurane, remifentanil and fentanyl, each of which is capable of exacerbating POD.[18–20]

In this study, we assessed the efficacy and safety of dexmedetomidine in reducing delirium after transthoracic oesophagectomy, a surgical intervention that is associated with an intense pro-inflammatory response.[7]

Methods

Study population and randomisation

The prospective single-centre, randomised, parallel-arm, double-blind study was conducted at Tongling People's Hospital of Anhui Medical University, People's Republic of China, Ethical approval for this study was provided by the Ethical Committee of Tongling People's Hospital of Anhui Medical University on 1 September 2016. The study protocol was registered with the Chinese Clinical Trial Registry (http://www.chictr.org.cn, ChiCTR-IPR-17010881). Following informed consent, elderly, (60 to 80 years) ASA I to III, patients scheduled for an open transthoracic oesophagectomy under general endotracheal anaesthesia were prospectively randomised to standard care [total intravenous anaesthesia (TIVA)] or to the intervention [dexmedetomidine with TIVA (DEX-TIVA)] groups. Exclusion criteria included patients with BMI more than 30 $kg\,m^{-2}$, severe pulmonary, cardiac, renal, hepatic, cerebrovascular comorbidities, chronic pain or substance abuse disorders, dementia or being treated with antipsychotic agents, allergy to dexmedetomidine and life expectancy less than 6 months.

An assistant, not involved in data collection, randomised the patients using a computer-generated randomisation programme and the assignments were kept in sealed opaque envelopes. On the morning of the surgery, the assistant opened a sealed envelope and prepared the dexmedetomidine or saline in identical syringes according to the group allocation. The anaesthesiologist who administered the injections, the investigators who assessed outcomes, as well as the patients were all blinded as to which group the patient had been allocated.

Anaesthesia and study drug administration

Following an 8-h fast, patients received an intravenous infusion of 10 $ml\,kg^{-1}$ lactated Ringer's solution while routine monitoring was established: this included pulse oximetry, ECG, invasive arterial blood pressure (BP), end-tidal carbon dioxide, and bispectral index (BIS; VISTA monitoring system; Aspect Medical Systems Inc., Norwood, Massachusetts, USA). The study drugs and placebo were diluted in 0.9% saline up to a volume of 50 ml in identical syringes yielding a concentration of dexmedetomidine of 1 $\mu g\,ml^{-1}$. A loading dose of dexmedetomidine, 0.4 $ml\,kg^{-1}$, bolus was administered over 15 min immediately prior to induction of anaesthesia, followed by a maintenance dexmedetomidine infusion of 0.1 $ml\,kg^{-1}\,h^{-1}$ until 1 h before the anticipated end of surgery. Anaesthesia was induced with midazolam (0.05 $mg\,kg^{-1}$), sufentanil (0.2 to 0.4 $\mu g\,kg^{-1}$), propofol (0.8 to 1.2 $mg\,kg^{-1}$) and muscle relaxation provided by rocuronium (0.6 $mg\,kg^{-1}$). After the onset of muscle relaxation, a left-sided double-lumen endotracheal tube was inserted under video laryngoscopy. Mechanical ventilation was initiated with a volume-controlled ventilation mode to achieve an end-tidal carbon dioxide content of 4.7 to 6.0 kPa (35 to 45 mmHg). Anaesthesia was maintained with infusions of propofol (4 to 6 $mg\,kg^{-1}\,h^{-1}$) and remifentanil (15 to 30 $\mu g\,kg^{-1}\,h^{-1}$). Muscle relaxation was maintained with intermittent doses of rocuronium. Intra-operatively, BIS values were maintained within 45 ± 5 by regulating the infusion rates of propofol and remifentanil. Patients received a continuous low-dose norepinephrine infusion and judicious fluid administration to maintain the mean arterial pressure (MAP) above 65 mmHg. Bradycardia (heart rate, HR $<$ 40 bpm) was treated with intravenous atropine 0.5 mg. Interventions for tachycardia ($>$120 bpm) and hypertension (systolic $>$180 mmHg or diastolic $>$100 mmHg) included adjustment of maintenance anaesthetics and vaso-active and cardio-active drug therapy. Propofol and remifentanil were discontinued at the time of wound closure. Postoperative analgesia was achieved with patient-controlled analgesia, which consisted of sufentanil according to body weight (3 $\mu g\,kg^{-1}$) and flurbiprofen axetil 150 mg (total volume including saline = 100 ml), delivered as 2 $ml\,h^{-1}$ background infusion and a bolus of 2 ml on demand with a 'lock-out' interval of 15 min, and 5 mg tropisetron for prophylaxis of postoperative nausea and vomiting. After the completion of surgery muscle relaxation was reversed, and the endotracheal tube was removed when

patients were able to follow verbal command to open their eyes.

Delirium assessment (primary exposure) and data collection

Emergence agitation was assessed 1 min after extubation and repeated every 5 min thereafter during the first 30 min in the postanaesthesia care unit (PACU) using the Riker Sedation Agitation (RSA) scale with RSA scores more than 5 being defined as emergence agitation. Assessment of delirium was performed twice daily (morning between 9:00 and 11:00 a.m., and afternoon between 3:00 and 5:00 p.m.) for 4 postoperative days by trained POD assessors using the confusion assessment method.[21] In addition, assessors reviewed medical records and asked the patients and their families for evidence of delirium including confusion, agitation, hallucinations, delusions and sedation during assessments. The POD assessors were blinded to treatment allocation.

The MAP and HR were continuously measured and recorded: before administration of dexmedetomidine or saline at baseline (T1); 15 min after the intervention but before induction (T2); after anaesthesia induction but before tracheal intubation (T3); immediately after tracheal intubation (T4); immediately after tracheal extubation (T5); on arrival in the PACU (T6); immediately before discharge from the PACU (T7).

Arterial blood samples (3 ml) were drawn into EDTA tubes before the intervention drug was infused (preoperatively) and at the end of the operation (postoperatively). The blood samples were centrifuged at $1000 \times g$ for 15 min. Serum samples were stored at $-80\,^{\circ}C$ until further analysis. Interleukin-6 (IL-6) was measured with ELISA kits (CUSABIO BIOTECH CO., Ltd., Wuhan, China).

Additional outcomes including surgical duration, one-lung ventilation duration, anaesthetic consumption, time to extubation after discontinuing propofol, PACU length of stay, and side-effects such as bradycardia, nausea, vomiting and shivering were recorded.

Sample size and statistical analysis

Two earlier studies had reported the incidence of POD in elderly patients undergoing transthoracic oesophagectomy as 42 and 50%.[22,23] Previous studies had reported that dexmedetomidine decreased the incidence of POD by 45 to 61% in comparison with placebo in elderly patients.[24,25] We conservatively estimated that the incidence of delirium would be 40% in TIVA group, that DEX-TIVA would reduce the rate to 20%, that is a 50% reduction and we allowed for a 10% dropout rate. Power analysis indicated 176 patients were required for a two-sided alpha of 5% with 80% power.

Continuous variables were expressed as mean ± SD for normally distributed data, tested by d'Agostino–Pearson omnibus normality test, and by median [IQR] if not normally distributed. A two-tailed Student's t test was used to determine statistical significance in continuous, normally distributed data. The Mann–Whitney U test was used for nonparametric data, and confidence intervals (CIs) for nonnormally distributed variables were calculated by Hodges–Lehmann estimator. Categorical variables were summarised as frequencies and percentages and analysed using χ^2 or Fisher's exact test. Intention-to-treat analyses (all patients) and per-protocol analyses (excluding patients who withdrew or were lost to follow-up) were used for the primary outcome of POD. For secondary outcomes, only per-protocol analysis was performed. The two groups were compared with χ^2 test; relative risk (RR) and CI for proportions were calculated at 95% level. Kaplan–Meier survival estimates were used to compare the differences in time to delirium. The haemodynamic data and proinflammatory cytokine IL-6 were analysed using two-way repeated-measures analysis of variance with Bonferroni correction for both within-group and between-group comparisons. P values less than 0.05 were considered statistically significant. Calculations and statistical analyses were performed using GraphPad Prism version 5.03 (GraphPad Software, San Diego, California, USA).

Results

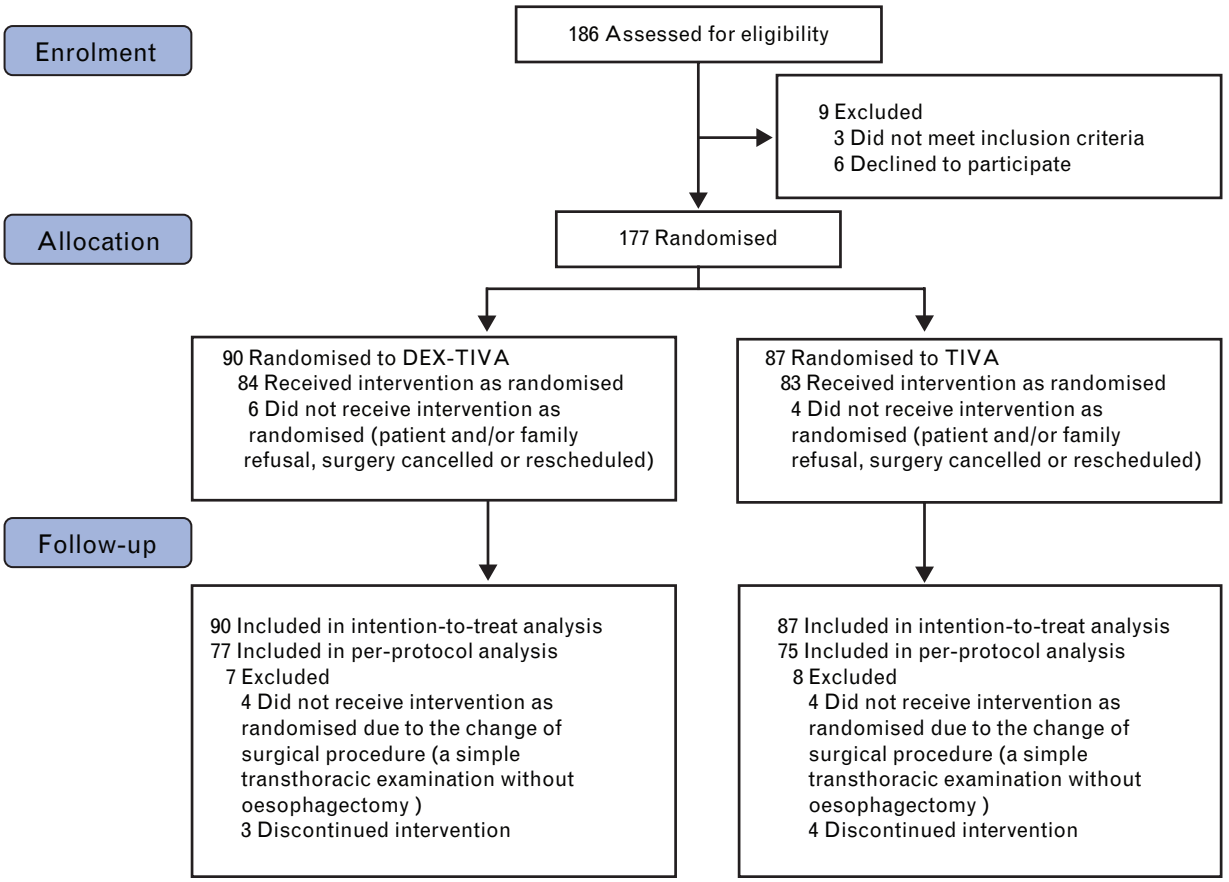
From November 2016 to September 2018 186 elderly oesophagectomy patients were screened: three met exclusion criteria and six refused to participate. The remaining 177 were enrolled into the trial with 90 assigned to the DEX-TIVA group and 87 to TIVA group. Ten patients (DEX-TIVA six; TIVA four) did not receive the allocated treatment due to surgical cancellation or other reasons, leaving 84 patients in the DEX-TIVA group and 83 patients in the TIVA group. In addition, seven patients dropped out after receiving dexmedetomidine and eight patients dropped out after receiving placebo. These 15 patients dropped out because of a change in surgery or bleeding more than 600 ml intraoperatively, or nonelective postsurgical ICU admission was required. A total of 152 patients completed the study (Fig. 1). The two groups were comparable with respect to demographic characteristics and showed no differences in pre-operative and intra-operative factors (Tables 1 and 2).

Primary outcomes

According to the intention-to-treat analysis ($n = 177$), delirium occurred in 16.7% (15/90) of cases in the DEX-TIVA group and in 36.8% (32/87) of cases in the TIVA group: RR, 0.45 (95% CI, 0.26 to 0.78); $P = 0.0036$ (Table 3).

According to the per-protocol analysis ($n = 152$), the DEX-TIVA group had a lower incidence of delirium within the first 4 postoperative days than the TIVA group 19.5% (15/77) vs. 42.7% (32/75), respectively; RR, 0.46

Fig. 1 CONSORT flow diagram.



DEX-TIVA, dexmedetomidine and total intravenous anaesthesia group; TIVA, placebo (saline) and total intravenous anaesthesia group.

Table 1 **Patient demographics**

Characteristic	DEX-TIVA, $n = 90$	TIVA, $n = 87$	*P*
Age (years)	69.6 ± 4.5	69.1 ± 5.1	0.5120
Male	75 (83.3)	71 (81.6)	0.8441
BMI (kg m^{-2})	21.5 ± 3.1	21.8 ± 2.9	0.5312
ASA grade			
I	20 (22.2)	16 (18.4)	0.7903
II	64 (71.1)	64 (73.6)	
III	6 (6.7)	7 (8.0)	
Smoking	27 (30.0)	31 (35.6)	0.5219
Hypertension	38 (42.2)	34 (39.1)	0.7598
Diabetes mellitus	14 (15.6)	13 (14.9)	1.0000
RCRI (Lee's score)	1.7 ± 0.7	1.7 ± 0.6	0.9310
Clinical TNM classification			
I	41 (45.6)	37 (42.5)	0.6319
II	45 (50.0)	48 (55.2)	
III	4 (4.4)	2 (2.3)	
Type of surgery			
Left transthoracic oesophagectomy (Sweet)	39 (43.3)	37 (42.6)	0.3977
2-Field abdominal-thoracic operation (Ivor–Lewis)	47 (52.2)	49 (56.3)	
3-Field cervical-thoraco-abdominal operation	4 (4.5)	1 (1.1)	

Data are presented as mean ± SD or number of patients (%). ASA, American Society of Anesthesiologists physical status; DEX-TIVA, dexmedetomidine and total intravenous anaesthesia group; RCRI, Revised Cardiac Risk Index; TNM, Tumour, Node, Metastasis classification system; TIVA, placebo (saline) and total intravenous anaesthesia group.

Table 2 Intra-operative and postoperative profiles

	DEX-TIVA, $n=77$	TIVA, $n=75$	Mean difference or relative risk	95% CI	P
EA	17 (22.1)	36 (48.0)	0.54	0.33 to 0.85	0.0058
Duration of surgery (min)	253 ± 78	258 ± 81	−5.03	−30.67 to 20.61	0.6989
OLV duration (min)	179 ± 47	182 ± 46	−2.87	−17.70 to 11.97	0.7033
Time to extubation (min)	5 [2 to 8]	5 [2 to 8]	0.00	0.00 to 1.00	0.8163
Fluid balance (ml)	1773 ± 394	1841 ± 384	−68.21	−192.80 to 56.43	0.2813
Blood loss (ml)	324 ± 92	318 ± 107	7.21	−24.67 to 39.09	0.6556
PACU stay (min)	77 ± 22	80 ± 25	−2.61	−10.25 to 5.02	0.4995
Propofol (mg)	987 ± 297	1097 ± 366	−109.50	−216.10 to −2.99	0.0440
Remifentanil (mg)	2.5 ± 0.7	2.9 ± 0.6	−0.34	−0.55 to −0.14	0.0009
Sufentanil (μg)	24 ± 4.0	25 ± 3.8	−0.08	−1.33 to 1.17	0.9003

Data are presented as mean ± SD, median [IQR] or number of patients (%). CI, confidence interval; DEX-TIVA, dexmedetomidine and total intravenous anaesthesia group; EA, emergence agitation; OLV, one lung ventilation; PACU, postanaesthesia care unit; TIVA, placebo (saline) and total intravenous anaesthesia group; Fluid balance, input (fluid) − output (blood loss + urine + chest tube drainage).

(95% CI, 0.27 to 0.77); $P=0.0027$ (Table 3), and the time to delirium in all participants also differed ($P=0.0046$) (Fig. 2).

To test the robustness of these findings, a sensitivity analysis was conducted by coding withdrawals after the oesophagectomy procedure as delirium positive in the DEX-TIVA arm and delirium negative in the TIVA arm. In this conservative scenario, the incidence of POD remained significantly different between groups, with a RR of 0.54 (95% CI, 0.33 to 0.89); $P=0.0189$ (Table 3).

Secondary outcomes

The DEX-TIVA group showed a decreased incidence of emergence agitation compared with the TIVA group, 22.1% (17/77) vs. 48.0% (36/75), respectively: RR, 0.54 (95% CI, 0.33 to 0.85); $P=0.0058$ (Table 2). The distribution histogram of the RSA scale of all patients at 1 min after extubation is shown (Fig. 3).

The concentration of IL-6 was comparable between groups at baseline. IL-6 increased significantly in both groups postoperatively although the incremental change was significantly smaller in the DEX-TIVA group (Fig. 4).

The intra-operative requirement for propofol in DEX-TIVA group was lower than in the TIVA group: median difference −109.50 (95% CI, −216.10 to −2.99) mg, $P=0.0440$. The consumption of remifentanil was also lower in DEX-TIVA group: median difference −0.34 (95% CI, −0.55 to −0.14) mg, $P=0.0009$. There were no differences in consumption of sufentanil between the two groups: median difference −0.08 (95% CI, −1.33 to 1.17) μg, $P=0.9003$ (Table 2).

The haemodynamic data during surgery and the PACU stay are presented in Fig. 5. MAP and HR were similar in both groups at baseline, but HR was significantly lower in the dexmedetomidine group than in the TIVA group at several time points (T2, T4, T5, T6). MAP was lower in the dexmedetomidine group at T4 only. The DEX-TIVA group demonstrated more stable haemodynamics during the induction, intubation and PACU stay period compared with TIVA group. When comparing the fluctuations of MAP, we found a larger variance in the TIVA group. The median [IQR] MAP variance in the TIVA group was 140.5 [97.4 to 226.2] $mmHg^2$ and in the DEX-TIVA group 131.8 [73.4 to 190.9] $mmHg^2$; the fluctuations of MAP were larger in the TIVA group than in the DEX-TIVA group ($P=0.0291$).

Safety outcomes

Apart from a lower incidence of shivering in the PACU in the DEX-TIVA group, there was no statistical difference in adverse events between the two groups (Table 4).

Discussion

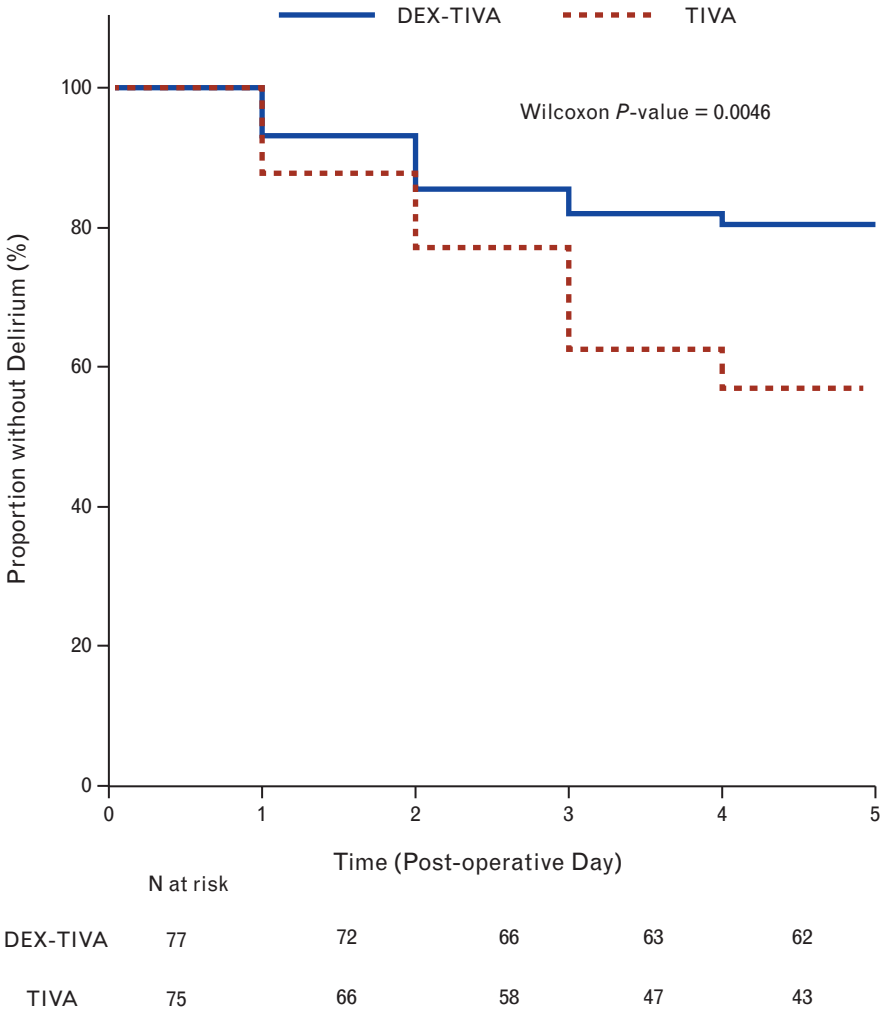
Our study shows that the addition of dexmedetomidine to a total intravenous anaesthetic safely reduces POD and emergence agitation in elderly patients undergoing open transthoracic oesophagectomy. These benefits were associated with a postoperative reduction in circulating levels

Table 3 Primary outcomes[a]

	Incidence of delirium, No./Total (%)			
Study population	DEX-TIVA	TIVA	RR (95% CI)	P
Intention to treat	15/90 (16.7)	32/87 (36.8)	0.45 (0.26 to 0.78)	0.0036
Per protocol	15/77 (19.5)	32/75 (42.7)	0.46 (0.27 to 0.77)	0.0027
Sensitivity analysis[b]	18/90 (20.0)	32/87 (36.8)	0.54 (0.33 to 0.89)	0.0189

Data are presented as number of patients (%). CI, confidence interval; DEX-TIVA, dexmedetomidine and total intravenous anaesthesia group; RR, relative risk; TIVA, placebo (saline) and total intravenous anaesthesia group. [a] The intention-to-treat group included all participants randomised without exclusions, analysed according to their original treatment group assignment. The per-protocol group excluded participants who withdrew or were lost to follow-up. [b] Recoding missing values owing to study withdrawals as delirium positive for the DEX-TIVA group or delirium negative for the TIVA group.

Fig. 2 Kaplan–Meier curves showing the time to delirium in all patents between dexmedetomidine and total intravenous anaesthesia group and placebo (saline) and total intravenous anaesthesia group undergoing surgery.

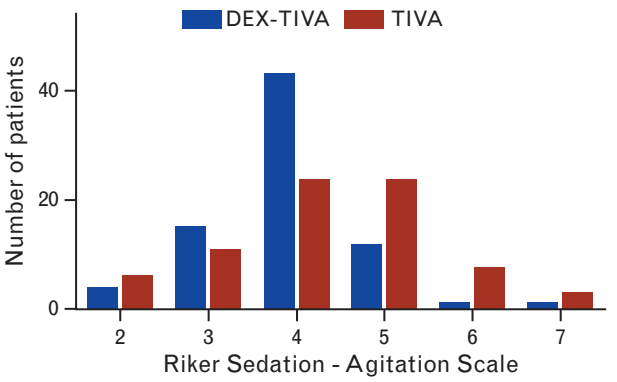


DEX-TIVA, dexmedetomidine and total intravenous anaesthesia group; *N* at risk, number of participants remaining at risk of developing postoperative delirium; POD, postoperative delirium; TIVA, placebo (saline) and total intravenous anaesthesia group.

of the pro-inflammatory cytokine IL-6 and stabilisation of the haemodynamic profile.

Previously published prospective studies revealed the incidence of POD after oesophagectomy to be ~42% and this was not significantly reduced by haloperidol.[23,26] In another study, there was a significant association between POD and the pre-operative Acute Physiology and Chronic Health Evaluation score.[27] In a retrospective study addressing POD and oesophagectomy in 1041 patients, the risk factors for delirium in the first days were; advanced age, pre-operative cerebrovascular disease, pulmonary dysfunction, transfusion and hydroxyethyl starch administration.[28] In a second retrospective study the incidence of POD was 50% after oesophagectomy, usually by postoperative day 3, and correlated positively with advancing age and male sex.[23] In our trial of predominantly male patients the mean age was 69.6 years, and the addition of dexmedetomidine reduced the incidence of POD from 42.7% (TIVA group) to 19.5% (DEX-TIVA group) during postoperative days 1 to 4; the decision to limit the assessment to this postoperative epoch was predicated by the need to avoid compounding the data with the delirium from surgical complications, such as pulmonary infection, sepsis or conduit leak, which typically occur after 3 or 4 days.[29] A recent report involving thoracic surgical patients revealed no reduction in POD with dexmedetomidine through postoperative day 3, although emergence agitation was reduced.[30] Possible reasons for the discrepancy between our study and that reported by Kim *et al.*[30] include the fact that we assessed patients for a longer period, that transthoracic

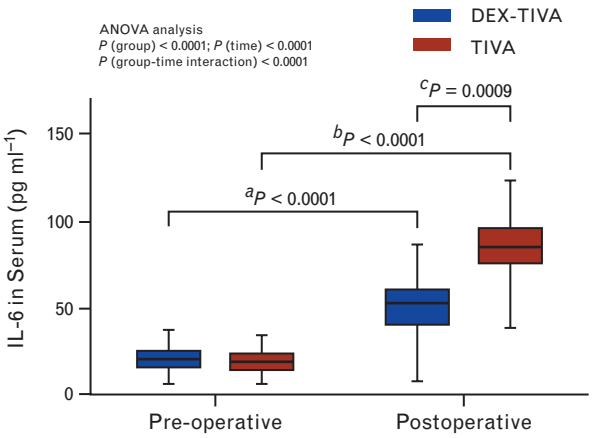
Fig. 3 Riker Sedation – Agitation Scale at 1min after extubation.



1, minimal or no response to noxious stimuli; 2, arousal to physical stimuli but noncommunicative; 3, difficult to arouse but awakens to verbal stimuli or gentle shaking; 4, calm and follows commands; 5, anxious or physically agitated but calms to verbal instructions; 6, requires restraint and frequent verbal reminding of limits; 7, attempting to remove tracheal tube or catheters, or striking out at staff. DEX-TIVA, dexmedetomidine and total intravenous anaesthesia group; TIVA, placebo (saline) and total intravenous anaesthesia group.

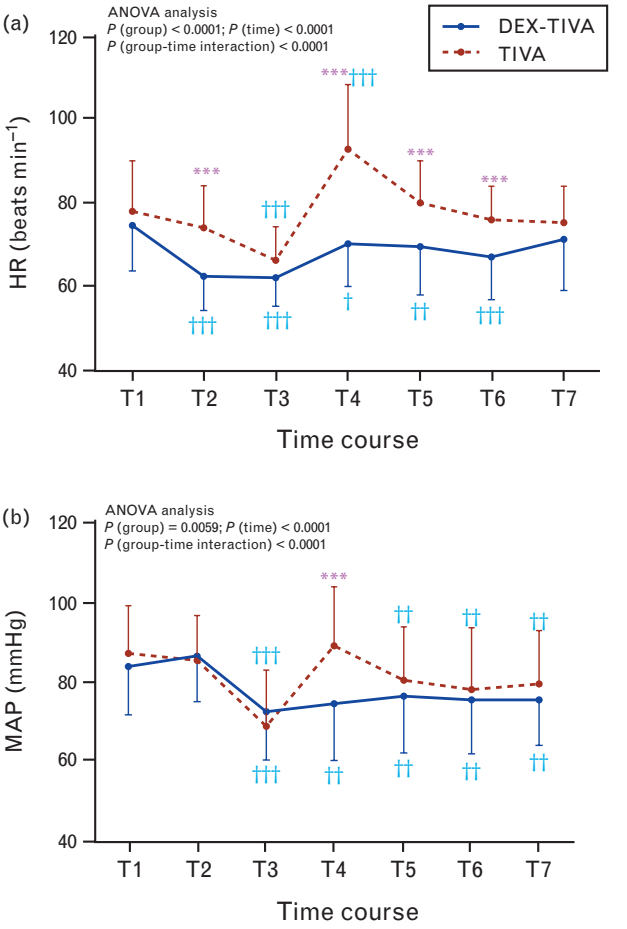
oesophagectomy is a more severe surgical insult than thoracoscopic lung resection surgery, and that our patients were older. That individuals undergoing oesophagectomy have a higher incidence of POD (32.1%) than those undergoing other thoracic surgeries (13.7%) has been reported previously.[26]

Fig. 4 Plasma concentrations of inflammatory cytokine IL-6 between pre-operative and postoperative in two groups.



The box shows the median [IQR], and the whiskers represent the minimum and maximum. (a) the concentrations of IL-6 in dexmedetomidine and total intravenous anaesthesia group at pre-operative vs. postoperative; (b) the concentrations of IL-6 in placebo (saline) and total intravenous anaesthesia group at pre-operative vs. postoperative; (c) the concentrations of IL-6 at postoperative in dexmedetomidine and total intravenous anaesthesia group vs. placebo (saline) and total intravenous anaesthesia group. DEX-TIVA, dexmedetomidine and total intravenous anaesthesia group; TIVA, placebo (saline) and total intravenous anaesthesia group.

Fig. 5 Haemodynamic data at various time points in all patients undergoing surgery in two groups. Heart rate (a); mean arterial pressure (b).



Data are expressed as mean ± SD. DEX-TIVA, dexmedetomidine and total intravenous anaesthesia group; HR, heart rate; MAP, mean arterial pressure; TIVA, placebo (saline) and total intravenous anaesthesia group. T1, baseline; T2, 15 min later after intervention before induction; T3, after anaesthesia induction before tracheal intubation; T4, after tracheal intubation immediately; T5, immediately after tracheal extubation; T6, transfer into postanaesthesia care unit; T7, transfer out of postanaesthesia care unit. $^{***}P < 0.0001$ vs. dexmedetomidine and total intravenous anaesthesia group; $^{\dagger}P < 0.05$, $^{\dagger\dagger}P < 0.001$, $^{\dagger\dagger\dagger}P < 0.0001$ vs. T1.

The data for the purported efficacy of dexmedetomidine for other noncardiac surgical patients are controversial. Deiner *et al.*,[31] in patients over the age of 68, assessed delirium daily while the patients were in hospital or until postoperative day 5: dexmedetomidine ($0.5\,\mu g\,kg^{-1}\,h^{-1}$), administered intra-operatively and continued until 2 h postoperatively, did not reduce the incidence of delirium, although the overall incidence was unusually low at just 11.8%, possibly because the exclusion criteria selected patients who were relatively well and less likely to develop delirium. On the contrary, as neither the depth of anaesthesia nor the consumption of anaesthetics (such

Table 4 Safety outcomes

	DEX-TIVA, $n = 77$	TIVA, $n = 75$	P
Bradycardia (HR < 40)	0 (0)	0 (0)	1.0000
Bradycardia with intervention	0 (0)	0 (0)	1.0000
Tachycardia	0 (0)	3 (4.0)	0.1177
Tachycardia with intervention	0 (0)	1 (1.3)	0.4934
Hypotension	42 (54.5)	32 (42.7)	0.1489
Hypotension with intervention	40 (51.9)	31 (41.3)	0.1983
Hypertension	4 (5.2)	5 (6.7)	0.7439
Hypertension with intervention	3 (3.9)	5 (6.7)	0.4916
Nausea	6 (7.8)	8 (10.7)	0.5856
Vomiting	0 (0)	0 (0)	1.0000
Shivering	4 (5.2)	12 (16.0)	0.0359

Data are presented as number of patients (%). DEX-TIVA, dexmedetomidine and total intravenous anaesthesia group; HR, heart rate; TIVA, placebo (saline) and total intravenous anaesthesia group.

as propofol, opioids and sevoflurane) were mentioned in that report, its results cannot be readily compared with other studies in which dexmedetomidine was administered intra-operatively. In a similar sized study to Deiner *et al.*,[31] Su *et al.*[25] ($n = 700$) reported that dexmedetomidine ($0.1\ \mu g\ kg^{-1}\ h^{-1}$) administered during the first night after surgery significantly reduced delirium in noncardiac surgical patients over the age of 65 years. The results of two meta-analysis have been published in the last year[32,33] and both indicated that dexmedetomidine significantly reduced the incidence of POD with approximately the same magnitude of change (i.e. 50%), as observed in the current study.

Emergence agitation, also known as emergence delirium, is typically noted immediately after awakening from general anaesthesia while the patient is in the PACU. In agreement with our results, recent studies also noted that dexmedetomidine decreased emergence agitation after thoracic surgery.[34,35] Given that 57% of patients in the DEX-TIVA group had an RSA score of 4, the reduction in emergence agitation could not be ascribed to the sedative effect of dexmedetomidine.

Intra-operative dexmedetomidine infusion limited the increase of pro-inflammatory cytokine, IL-6, after surgery. In both preclinical surgical models and in clinical trials dexmedetomidine exhibited significant anti-inflammatory properties.[36–38] It is notable that the addition of dexmedetomidine did not alter the postoperative inflammatory response when patients received regional anaesthesia,[39] an anaesthetic technique that attenuates the surgery-induced pro-inflammatory response.[40] While the mechanism for the anti-inflammatory effect is not well defined in humans, dexmedetomidine in a preclinical model demonstrated significant cholinergic-mediated inflammation-resolving properties.[17,41]

Peri-operative administration of α_2-adrenergic agonists provide haemodynamic stability[42] which was also demonstrated in our study: in the TIVA group there were moderate elevations of HR and BP postintubation and intra-operatively which were attenuated in the DEX-TIVA group. While the HR tended to be slower in the DEX-TIVA group, no serious bradycardia requiring intervention was noted intra-operatively. Significantly, in a large cohort of older patients intra-operative fluctuations in haemodynamic variables were correlated with the subsequent development of POD.[43] Haemodynamic stability may be obtained with dexmedetomidine through a blunting of the stress response as evidenced by a decrease in the release of catecholamines intra-operatively.[38]

Pain, and the use of anaesthetic agents and opioids are among the risk factors for POD and emergence agitation.[2,44] In our study, dexmedetomidine reduced consumption of propofol and opioids while maintaining similar BIS levels of anaesthesia in two groups. A combination of all the above benefits of dexmedetomidine may have contributed to the reduced incidence of POD and emergence agitation.

Limitations

There are several limitations to our study. First, our inclusion/exclusion criteria selected surgical patients who were expected to have a higher risk of POD and emergence agitation because of their older age, male sex and type and duration of pain associated with transthoracic oesophagectomy surgery. Second, according to POD prevention guidelines, managing pain, mobilisation and sleep during the postoperative period is crucial in postoperative management;[45] these were not recorded in our study and therefore it is possible that the groups may not have been matched for these risk factors. Thirdly, the study was performed in a single centre, and this limits its generalisability. Neither ASA IV patients nor those expected to be admitted postoperatively to the ICU were included. While there was no difference in the frequency of adverse events between the two groups, this study is underpowered to detect a small but statistically significant difference in adverse events.

Nonetheless, the strengths of our study include twice-daily delirium assessment, and the blinded nature of the trial which reduced investigator bias.

Conclusion

We conclude that the intra-operative infusion of dexmedetomidine decreases POD and emergence agitation while maintaining haemodynamic stability in elderly patients undergoing open transthoracic surgery. Patients who received dexmedetomidine had reduced consumption of anaesthetics and an attenuated surgery-induced IL-6 response.

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Conflicts of interest: MM is a co-inventor on a patent for the use of dexmedetomidine for sedation. MM has not and will not receive royalty payments for sales of dexmedetomidine. The other authors declare no competing interests.

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