Aus der Klinik für Anästhesiologie mit Schwerpunkt operative Intensivmedizin
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DISSERTATION

Delirprävention bei älteren Patienten durch intraoperative Gabe von Dexmedetomidin bei Hochrisikoeingriffen

Prevention of delirium by intraoperative administration of Dexmedetomidine to elderly patients during high-risk surgery

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POD	Postoperative Delirium
POCD	Postoperative Cognitive Dysfunction
CABG	Coronary Artery Bypass Grafting
ICU	Intensive Care Unit
PACU	Post Anesthesia Care Unit
RCT	Randomized Controlled Trial
CAM	Confusion Assessment Method
CAM-ICU	Confusion Assessment Method for the ICU
RR	Risk Ratio
bpm	beats per minute
RASS	Richmond Agitation-Sedation Scale
h	hour
min	minute
aMCI	amnestic mild cognitive impairment

Abstract

Introduction

Postoperative Delirium (POD) is a fluctuating and faltering state of the brain characterized by deficits in attention, cognition, and awareness. It forms a major independent predictor for Intensive Care Unit (ICU)-mortality in elderly people as 1-year ICU survival probability decreases by 10% for every day spent with POD. Since its introduction in 2011, dexmedetomidine has proven to be a potent α2-agonist effective in the treatment of delirium on ICUs with translational rat studies indicating an anti-inflammatory and mortality-reducing effects when given simultaneously to a systemically induced (neuro-)inflammation. This raises the question whether perioperative administration of dexmedetomidine (both intra- and postoperative) could reduce the rate of POD. By the beginning of our trial in July 2014, in which we randomized 63 patients to dexmedetomidine or placebo, Randomized Controlled Trials (RCTs) regarding this subject had yet to be published. This dissertation tries to answer this question by discussing our trial and comparing it to the latest RCTs and literature.

Methods

First an extensive review of the literature was done to explore the facets of delirium, the working mechanisms of dexmedetomidine and a review of the gold standard delirium screening tool CAM/CAM-ICU (Confusion Assessment Method for the general and ICU ward respectively). Then an in-depth review of our trial will follow in which will be focused on the incidence of POD in our dexmedetomidine and placebo groups and its β -blocker, non- β -blocker, cardiac and non-cardiac surgery strata, measured by CAM/CAM-ICU. To compare our trial to the latest body of evidence, a PUBMED search ("(Dexmedetomidine OR Dexdor) AND (Delirium OR delirious) AND (peri-operative OR perioperative OR intraoperative OR intra-operative)") was done to screen for the latest RCTs and meta-analyses.

Results

Including our trial, the majority of non-cardiac RCTs (13 out of 16) showed a significant reduction of POD in their respective dexmedetomidine groups, with various dosing and timing strategies. Although 3 out of 6 cardiac RCTs found a significant reduction, there was a lack of methodologically sound studies to properly evaluate the effect of intraoperative administered dexmedetomidine for cardiac surgery patients.

Conclusion

The current body of evidence suggests that, when selected for age (≥ 60 years) and scope of surgery with a foreseeable longer stay on the ICU, the administration of dexmedetomidine could lead to a significant reduction in POD for non-cardiac surgery patients. A new meta-analysis is needed to give a definitive answer. For cardiac surgery though, the evidence remains unclear and more and especially methodologically sound studies are needed.

Zusammenfassung

Einleitung

Das POD ist ein fluktuierender und mangelhafter Zustand des Gehirns, gekennzeichnet durch Defizite in Aufmerksamkeit, Kognition und Bewusstsein. Jeder Tag, den ein(e) PatientIn auf der Intensivstation mit Delir verbringt, senkt die 1-Jahres-Überlebenswahrscheinlichkeit um circa 10%. Seit dessen Introduktion im Jahr 2011 hat Dexmedetomidin sich als potenter α2-Agonist und als effektive Therapie für das POD erwiesen. Translationale Studien mit Ratten deuten auf anti-inflammatorische und mortalitätsreduzierende Effekte des Medikaments hin, wenn es gleichzeitig zu einer systemisch induzierten (Neuro)-Inflammation verabreicht wird. Dies wirft die Frage auf, ob sich durch perioperative Gabe (sowohl intra- als auch postoperativ) von Dexmedetomidin die Rate des PODs reduzieren lässt. Vor dem Beginn unserer Studie im Juli 2014, in welcher wir 63 Patienten zur intra- und postoperativen Gabe von Dexmedetomidin oder Placebo randomisierten, gab es noch keine veröffentlichten RCTs zu diesem Thema. Diese Dissertation versucht anhand unserer Studie und dem Vergleich der aktuellsten RCTs diese Frage zu beantworten.

Methodik

Zuerst wird ein ausführlicher Rückblick der verfügbaren Literatur gegeben, worin die Facetten des Delirs, die Arbeitsmechanismen des Dexmedetomidins und eine Bewertung des Goldstandard Delir Screening-Tools CAM/CAM-ICU dargestellt werden. Darauf folgt eine ausführliche Beschreibung unserer Studie, mit Fokus auf die Methodik und POD-Inzidenz unserer Dexmedetomidin- und Placebo-Gruppen und deren Strata (β -Blocker, ohne - β -Blocker, kardiochirurgisch und nichtkardiochirurgisch). Zum Recherche der aktuellsten Studienlage wurde eine PUBMED Suche (“(Dexmedetomidine OR Dexdor) AND (Delirium OR delirious) AND (peri-operative OR perioperative OR intraoperative OR intra-operative)”) durchgeführt, um unsere Studie mit den letzten RCTs zu vergleichen.

Ergebnisse

Inklusive unserer Studie fand die Mehrheit der nichtkardiochirurgischen RCTs (13 von 16) eine signifikante Reduktion der POD-Inzidenz in deren Dexmedetomidin-Gruppen. Obwohl 3 von 6 kardiochirurgische RCTs eine signifikante Reduktion der Dexmedetomidin-Gruppe aufwiesen, mangelte es an Studien mit ausreichender methodischer Qualität, um für diese Patienten eine eindeutige Aussage treffen zu können.

Schlussfolgerung

Die aktuelle Datenlage deutet darauf hin, dass innerhalb eines vorselektierten Patientenkollektivs hinsichtlich Patientenalter (≥ 60 Jahre) und Operation (großchirurgische Eingriffe mit einer voraussichtlich längeren Intensivverweildauer) die Gabe von Dexmedetomidin zu einer signifikanten Reduktion des PODs für nichtkardiochirurgische Patienten führen könnte. Um eine definitive Aussage für diese Patienten treffen zu können, ist allerdings noch eine aktuelle Meta-Analyse erforderlich. Für kardiochirurgische Patienten mangelt es derzeit jedoch an qualitativ verwertbaren Studien, um diese Frage beantworten zu können.

1. Introduction

1.1 Postoperative delirium and dexmedetomidine as a possible means for prevention

POD is a faltering state of the brain, for which especially elderly people are susceptible as predisposing factors tend to develop with age. Its symptoms are fluctuating during the day, characterized by an acute onset with deficits in attention, cognition and awareness and usually peak between postoperative day one to three[1, 2]. As 1- year survival probability of ICU-patients decreases by 10% for every day spent with POD[3], it forms a major predictor for ICU-mortality and stresses the importance of early treatment. A recent meta-analysis reviewed 71 studies that compared the odds ratio of ICU-mortality in delirious elderly (≥65y) patients to non-delirious controls[4], in which an odds ratio for mortality of 7.1 to 3.2 respectively was found. The authors mention that, despite advancements in delirium research, delirium in-hospital odds of mortality have not changed in the last 30 years. Moreover, it prolongs hospital stay by up to 10 days, worsens treatment outcomes and puts patients at risk for prolonged cognitive impairment, also known as Postoperative Cognitive Dysfunction (POCD) [5-7].

After its introduction in the European Union 2011[8], dexmedetomidine has proven to be a potent α2-agonist effective in the symptomatic treatment of delirium on ICU's [9]. As translational studies started to show the anti-inflammatory and mortality-reducing properties of dexmedetomidine in rat models when dexmedetomidine was given simultaneously to a systemically induced inflammation process [10,11] and a theory about the connection between systemic inflammation and delirium was developed [12], the curiosity into the prophylactic potential of dexmedetomidine with regards to POD was piqued. To shed a light on the potential of intraoperatively administered dexmedetomidine for patients as well our department for anaesthesiology developed a RCT to answer this question [13]. At the start of our trial in July 2014, RCTs that focused solely on both the intra- and postoperative administration of dexmedetomidine had yet to be published. This dissertation will provide a more in-depth analysis of the incidence of POD in our study and will compare it to the latest RCTs.

1.2 Intraoperative triggers and predisposing factors for delirium

Intraoperatively, delirium can be triggered by any type of inflammation (like systemic inflammation after major surgeries, sepsis or pre-existing local inflammation or infection), the use of anticholinergic drugs, sleep deprivation, occurrence and duration of burst-suppression on EEG-Monitoring [14], pain, electrolyte and acid-base disorders and the use of prodelirogenic medication like sedatives and opiates [15]. One must be aware though, that as so many different aetiologies are present, it is very unlikely that a single mechanism is at play. Moreover, predisposing factors can play a role, such as age above 65 years (especially above 75 years[16]), dehydration and malnutrition, polypharmacy (5 drugs or more), a history of alcohol or nicotine abuse, acute intoxications, pre-existing cognitive impairment based on brain injury, psychiatric illness or dementia, severe audiovisual impairments, as well as other pre-existing comorbidities such as severe liver or heart failure and chronic kidney disease[17].

1.3 The pathophysiology of delirium

In recent years, more is discovered about its pathophysiology and the self-propelling neuroinflammatory reaction that, amongst others, lies at the base of the disorder[12]. In their inflammation hypothesis (later referred to as neuroinflammatory hypothesis), van Gool at al. posed that pro-inflammatory cytokines, like IL-1β, IL-6, and TNF-α, play an important role in the activation of microglia after having passed the blood-brain-barrier (see figure 1). As microglia are the protagonists in the brains innate immune response, they can produce inflammatory mediators that not only regulate this response, but also weaken the tight junctions between astrocytes and affect neuronal function. These inflammatory mediators are toxic and can cause collateral damage to neighbouring neurons. Thus, van Gool et al. postulate that in this manner the brain becomes an engine of inflammation itself.

So far, several experimental models with rats showed the effects of induced systemic inflammation on neuroinflammation. For example, Qin et al. demonstrated that a systemically induced neuroinflammation through the peripheral injection- of lipopolysaccharide led to neuronal loss of up to 40% of the substantia nigra after 10 months[11].

Furthermore, it is hypothesized that these cytokines and chemokines can initiate a cascade that can lead to endothelial damage, thrombin formation and microvascular compromise of the brain and blood-brain barrier[18]. In addition, (after disease processes like trauma or surgery) leukocytes are released systematically, that adhere to endothelial cells of the blood-brain-barrier and degranulate, increasing the permeability even further[19].

In addition, age - especially in patients of 60 years and older - plays a major role in the chance of developing a POD: there is a decrease in cholinergic function with healthy ageing, being even more pronounced in Alzheimer's Disease, which results in less cholinergic inhibition of microglia and may play an important role in the pathogenesis of delirium[20]. This is also being referred to as the "neuronal aging hypothesis"[19]. An experimental rat study showed, that in previously vagotomized rats that received prophylactic administration of dexmedetomidine shortly before induction of systemic inflammation and neuro-inflammation, no downregulation of the cytokine response was found[21]. These findings suggests that the anticholinergic anti-inflammatory pathway plays a major role in downregulating pro-inflammatory cytokines, therefore reducing the chances of developing a delirium. Blocking the anticholinergic pathway by vagotomy and the prophylactic administration of dexmedetomidine turns out to be ineffective. This also stresses the need for careful consideration of the anticholinergic load of medication often used by the elderly population which can otherwise further increase the incidence of delirium.

Meanwhile, many theories have been posed next to the neuroinflammatory and neuronal aging hypothesis, e.g., oxidative stress, neurotransmitter deficiency, neuroendocrine diurnal dysregulation, as well as the network dysconnectivity hypothesis. An elaborate review of these hypotheses and their possible intersections has been published by Moldonado [19]. As he states in his article, none of these theories can explain the full etiology and rather must be seen as complementary. Therefore, the pathophysiology remains highly complex, multifactorial and to this day not fully understood.

1.4 Dexmedetomidine and its working mechanism

Dexmedetomidine is a highly potent α2-agonist with sedative, antisympathetic, coanalgetic and anxiolytic effects. It has several advantages over other sedatives for the management of delirium: it displays sedative properties without respiratory depression, has no anticholinergic effects, reduces the need for prodelirogenic agents such as sedatives, opioids and hypnotics [22–24] and promotes a more physiologic sleep-wake cycle in animal models[26]. Its antisympathetic effects are mirrored by an intraoperatively stable lower heart rate, typically found in these patients during continuous infusion of dexmedetomidine[13,26]. Furthermore, it reduces the incidence of postoperative shivering[27], which can drive the bodies metabolic rate up to 400% and can be especially dangerous for patients with a cardiopulmonary high-risk profile[29]. Its potential for

symptom control has already been widely investigated, but its potential for the prevention of POD as prophylactic agent by means of intraoperative administration is still subject of debate.

So far, several rat models were able to demonstrate a neuroprotective effect of dexmedetomidine[29–31]. By administering dexmedetomidine simultaneously to induction of systemic inflammation, an attenuation of the neuroinflammatory response could be shown as well as an attenuation of neurocognitive changes and prevention of excessive microglial hyperactivation. The exact mechanism of action is not yet fully understood, but inter alia involves the downregulation of pro-inflammatory cytokines like TNF-α IL1-β, which in turn prevents activation of the resting microglia and therefore lowering the chance of developing a delirium (see figure 1)[32,33]. Later, human studies were able to confirm the downregulation of TNF-α by intraoperative administration of dexmedetomidine as well[34,35]. Furthermore, dexmedetomidine is shown to work through the cholinergic pathway as well: as shown by mice studies, dexmedetomidine modulates the secretion of inflammatory cytokines through a2-adrenergic receptors on macrophages and monocytes and inhibit the synthesis of nuclear factor-κB by activating the cholinergic anti-inflammatory pathway[36].

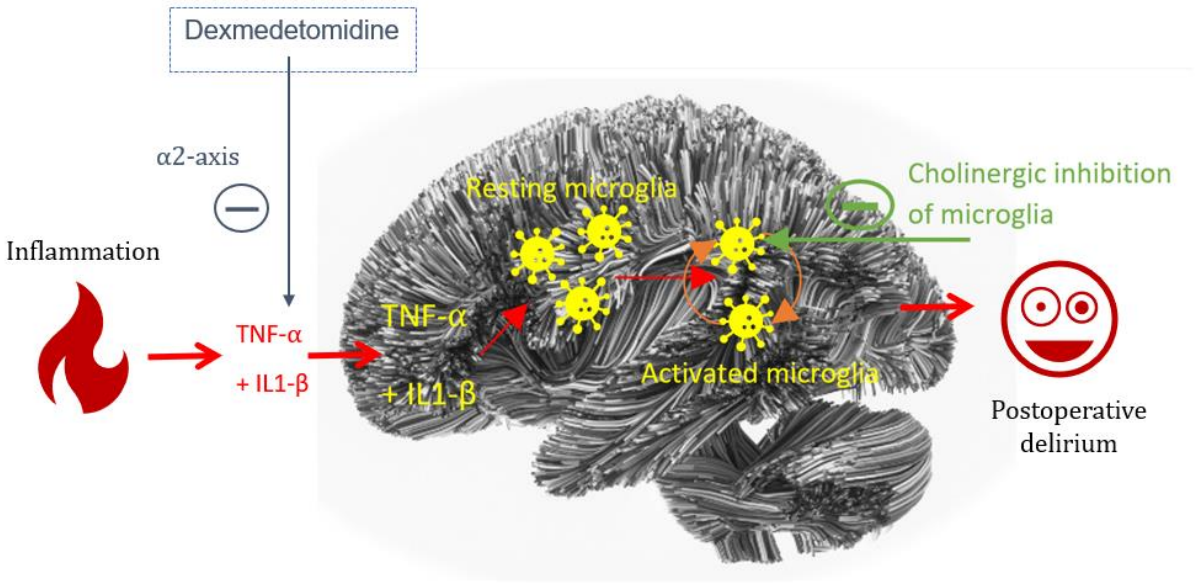

Figure 1: Dexmedetomidine and its mechanism of action, authors own depiction

In addition, dexmedetomidine has the potential to promote a physiological sleep-wake cycle and has inhibitive effects on almost all parts of the brain, especially the nucleus coeruleus[37]. By acting on the latter, dexmedetomidine inhibits the release of norepinephrine, which causes

Gamma-aminobutyric acid (GABA) output from the ventrolateral preoptic nucleus and inhibition of the neurotransmitters of wakefulness to produce a Non-rapid eye movement (NREM) sleep pattern[38]. Furthermore, dexmedetomidine was shown to have co-analgetic properties by acting on the α_2-receptors of the substantia gelatinosa of the dorsal horn of the spinal cord where it reduces the release of transmitters involved in nociception[39].

In addition, dexmedetomidine is thought to work through the reduction of serum cortisol levels as well. Studies have shown that serum levels of cortisol are highly correlated with an increased risk for POD [40]. Under stressful conditions the brain is known to promote adrenocortical function via hypothalamic corticotrophin-releasing hormone. This is partially counteracted by a negative feedback-mechanism on the hypothalamus. There are glucocorticoid receptors on the hippocampus and frontal lobe that are closely associated with cognition. Glucocorticoids have a U-shaped dose response relationship: memory is impaired by sustained glucocorticoid levels that are either too high or too low but improved by proportional glucocorticoid levels[41]. Li et al. (2016) were able to demonstrate, that serum cortisol levels in patients undergoing open gastrectomy were significantly lower at the time of coeliac exploration and after extubation in patients that received dexmedetomidine intraoperatively compared to placebo[42]. This reduction, however, was not achieved amongst patients in their dexmedetomidine epidural subgroup. Therefore, the reduction of cortisol shows another mode of action in the prevention of POD, especially in the absence of epidural anesthesia. This was later confirmed by Lee et al. who were able to show a significant reduction in 1-hour postoperative serum cortisol levels in patients that intraoperatively received dexmedetomidine during laparoscopic major non-cardiac surgery [43].
Finally, findings by the study of Xin et al. indicate dexmedetomidine might work through reduction of the permeability of the blood-brain barrier in patients with mild cognitive impairment[34]. They therefore argue that this mechanism may play a role in the reduction of neuroinflammation.

1.5 Side effects and safety

The most common side effects of dexmedetomidine are a result of the biphasic haemodynamic effects of dexmedetomidine, particularly after a loading dose: it initially might produce hypertension by acting on the α_2-receptors of the vascular smooth muscle, followed by hypotension and bradycardia as a result of central noradrenaline release[44]. In a meta-analysis by Wang et al. that looked at 18 RCTs with 1730 patients in total, the efficacy and safety of

perioperative (mainly postoperative) dexmedetomidine administration in cardiac surgery patients was analysed[45]. They found the incidence of hypotension to be comparable between the dexmedetomidine and placebo group. Moreover, incidences of POD and myocardial ischaemia were found to be significantly lower in the dexmedetomidine group. It concluded that dexmedetomidine can effectively reduce the incidence of early POD and ventricular tachycardia after cardiac surgery with tolerable adverse events and therefore confirmed its efficacy and safety for use in the ICU. However, as only studies regarding the post-operative administration of dexmedetomidine were analysed, an evaluation regarding its efficacy and safety if administered intra-operatively is still needed. Indeed, 2 out of 6 recent cardiac RCTs with intraoperatively administered dexmedetomidine did raise some concerns about its safety, as a non-significant ($p > 0.05$) increase in POD in the dexmedetomidine group was observed[46,47].

1.6 Hypothesis

We hypothesized, that the intraoperative administration of dexmedetomine would lead to a reduction in POD from 45% to 10% in comparison to the administration of a placebo[48,49].

2. Methods

2.1 Study Design of our trial

To properly study the effects of intraoperative administration of dexmedetomidine a randomized, double blind controlled phase-IV trial was designed, in which was focused on high-risk patients undergoing high-risk surgeries. The goal was to achieve neuroprotection with dexmedetomidine for patients undergoing elective cardiac or abdominal surgery. Hence the trial was registered as the Neuprodex trial. It was conducted from July 2014 to July 2018 at the department of anesthesiology and operative Intensive Care Medicine at 2 campuses of the Charité: Charité Virchow Klinikum and Charité Campus Mitte. The study was approved by the by the Federal Institute for Drugs and Medical Devices (BfArM) (registration number: 4039307) on September 13th, 2013, and the by Ethics Committee of the Department for Health and Social Affairs (LaGeSo) (registration number: 13/0491-EK11) on January 30th, 2014 and was registered at clinicaltrials.gov (NCT02096068).

2.2 Participants

The study focused on high-risk patients of 60 years and older with a foreseeable longer stay on the ICU because of high-risk surgeries (major elective cardiac or abdominal surgery, see below).

Patients were randomized into 4 groups according to location of surgery (cardiac and abdominal) and whether patients were on β-blocker therapy or not. It is known that stimulation of the β1-receptor increases intracellular cyclic adenosine monophosphate (cAMP), which can induce a reduction of inflammatory cytokines like TNF-α and IL-1β and can increase anti-inflammatory cytokines like IL-10. [50,51]. To analyse the possible influence of β-blocker therapy on treatment outcome, patients were stratified according to whether they received β-blocker therapy or not as well. Eligible patients were asked for study participation during preoperative screening on the anesthesia outpatient clinic one or several days before surgery by the studies clinical research physicians. In German these are called 'Prüfärzte' which were physicians that successfully completed a Good Clinical Practice course (a prerequisiste in Europe to be allowed to perform clinical trials), in which they learned about all the facets of performing clinical trials and their legal framework. Patient data and delirium scores (see below) were collected by trained research-assistants on Case Report Forms (CRFs).

2.3 Inclusion Criteria

Major elective cardiac or abdominal surgery was defined as elective CABG-surgery without valve surgery, done under cardiopulmonary bypass, with a left ventricular ejection fraction ≥ 30% or pancreatic, hepatic or intestinal surgery. According to the German Drug Law § 40 (1) 3b patients were offered information, and written informed consent was obtained prior to study inclusion.

The intraoperative administration of different kinds of medication was standardized: for premedication and management of postoperative anxiety only benzodiazepines were allowed. Furthermore, propofol or volatile anesthetics were used as standard hypnotic agents, and perioperative pain management was done by epidural anesthesia and/or intraoperative administration of sufentanyl/fentanyl, according to the S3-Guideline on Analgesia, Sedation and Delirium management in Intensive Care Medicine[52]. Instead of atropine, orciprenaline was used to avoid extra anticholinergic load (see figure 1).

Patients were excluded in case of known drug intolerance/allergies to ingredients of the placebo or verum, patient's objection to the use of their pseudonymized data, accommodation in an institution due to an official or judicial order, being an employee of the Charité University Hospital, illiteracy, lack of proficiency in the German language, Minimal mental Status Examination (MMSE) score below 24, severe hearing loss or visual impairment, acute brain injury, intracranial hemorrhage within a year before study participation, manifest psychiatric

disease, known illicit drug abuse, acute intoxication, pregnancy, homelessness, participation in concurrent interventional clinical trials, hemodynamic insufficiency at the time of inclusion (defined as a mean arterial pressure below 55 mm Hg despite vasopressors and optimization of preload), second- or third-degree atrioventricular block (AV-block), bradycardia below 50 bpm during resting state, spinal cord injury with known autonomic dysfunction, previous cerebrovascular accidents with neurological residue, liver cirrhosis with Child C or Model of End-stage Liver Disease (MELD) score above 17, intraoperative administration of remifentanil, administration of clonidine during administration of the study drug, planned postoperative sedation of RASS -4 to -5, or additional administration of dexmedetomidine within 3 months after inclusion.

2.4 Ordering of the study drug and randomisation process

After obtaining written informed consent the study drug was ordered at the hospitals apothecary on the day prior to surgery or on Fridays if the surgery was scheduled for a Monday. Here the study drug was prepared, which consisted of a syringe labelled with the patients' pseudonym, which was generated by a statistician from the "Institute for Biometrics and Clinical Epidemiology" (iBikE) at the Charité. The first arm received Dexmedetomidine from a 50ml syringe which contained 4µg/ml of Dexmedetomidine. The second arm received a 50ml syringe containing a 0.9% sodium chloride solution. All syringes were also provided with an envelope, which offered the possibility to unblind in case of emergency.

2.5 Administration of investigational drug

The clinical research physician received the investigational drug by the apothecary´s assistant and was present during the induction of general anesthesia. The prefilled syringe was put into a perfusor, connected to the patients' intravenous access via a perfusor line and started 10 minutes after induction (successful intubation) of anesthesia. When it contained dexmedetomidine, patients would receive a starting infusion rate of 0.7 $\mu g \cdot kg^{-1} \cdot h^{-1}$ dexmedetomidine with weight calculated as Adjusted Body Weight (ABW).

ABW was calculated as follows:
ABW = Ideal Body Weight (IBW) + 0.4 x (body weight – IBW)
IBW = 0.9 x (body height in centimeters – 100).

The infusion rate was reduced 30 minutes prior to the expected extubation time to 0.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$. On arrival on the ICU/PACU further administration rates were adjusted to achieve a Richmond Agitation-Sedation Scale (RASS) of -1/0. This was achieved by increasing or reducing the infusion rate in steps of 0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ every 20 minutes depending on the presence of oversedation (RASS < -1) or agitation (RASS > 0), up to a maximum of 1.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$.
If intraoperatively bradycardia and/or hypotension was present, and these could not be optimized by increasing preload and/or the use of vasopressors or orciprenaline, the infusion rate was reduced to 0.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and consecutively 0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ if necessary. In this case the infusion rate was not reduced 30 minutes prior to extubation and only reduced after arrival on the ICU/PACU. If the patient showed signs of oversedation, the infusion was paused for a maximum of 30 minutes. In case the patient was not directly extubated postoperatively the infusion rate, after arrival on PACU/ICU, was titrated with steps of 0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ to achieve a RASS of -1/0. Dexmedetomidine administration however was limited to a maximum of 48 hours.

To avoid intraoperative oversedation, every patient received EEG-Monitoring (Sedline®, Massimo, Irvine, CA, USA). Anesthetists were instructed to keep the Patient State Index above 25, avoid burst suppression, and to adjust the administration of hypnotic agents or opiates accordingly.

2.6 Primary endpoint of our trial

To be able to quantify the rate of POD we used the screening tool that is the gold standard for the screening of delirium: the CAM-ICU (Confusion Assessment Method for ICU patients) for patients on the ICU and the Confusion Assessment Method (CAM) that was modified for patients residing on a normal ward. Delirium can be subdivided into three forms: hypoactive (43.5%), hyperactive (1.6%) and mixed (54.9%)[53]. Whereas the hyperactive form goes easily recognisable, with patients being agitated, uncooperative, aggressive, and combative, hypoactive delirium and hypoactive phases of the mixed delirium are much harder to detect. These patients often get unrecognised or are considered sedated or depressed. Therefore, a screening tool is needed to identify a possible delirium in these patients.
The CAM-ICU enables the physician to screen for delirium within 60-90 seconds and can easily be learned by ICU-nurses as well[54]. Figure 2 shows the English version[55]. For our German study population, we used the German adaptation in which the word 'SAVEAHAART' is replaced by 'ANANASBAUM' and the questions regarding disorganized thinking are translated in German and 'Kilo' is used instead of 'pound'. In a CAM-ICU validation study by Ely et al. amongst 471

daily-paired evaluations by two nurses, a sensitivity of 93%-100% and specificity of 98%-100% was found[56]. This was also evaluated by our colleagues Luetz et al. who published a prospective cohort validation study amongst 156 surgical patients of 60 years or older and found a sensitivity of 81% and specificity of 96%[48]. A meta-analysis of Gusmao-Flores et al. evaluating the CAM-ICU amongst nine studies (n=969) calculated a pooled sensitivity of 80% and a specificity of 95.9%[57]. This is better than the Intensive Care Delirium Screening Checklist (ICDSC) for which the authors found a pooled sensitivity of 74% and specificity of 81.9%. For this reason, the CAM-ICU/CAM is the gold standard and used in our study as primary endpoint.

The Screening took place twice a day up to the fifth postoperative day and a last time on either the day of discharge or on the 14th postoperative day the latest. Additionally, to screen for possible missed episodes of delirium, a chart review was performed.

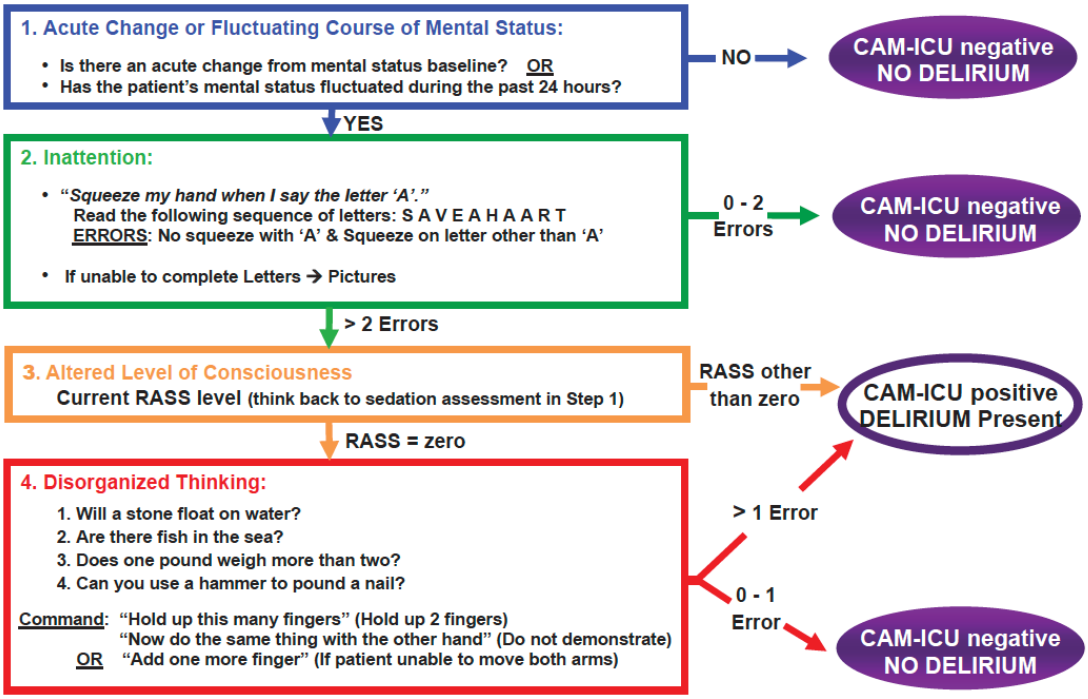

Figure 2: English version of the CAM-ICU screening algorithm[55]

2.7 Patient safety

Adverse reactions (AEs) and Severe Adverse reactions (SAEs) were being monitored until the fifth postoperative day after the first administration of investigational product (verum/placebo) by the studies clinical research physicians. The clinical research physician reported these on CRFs which were then discussed with the assigned monitor of the study and incorporated into

safety reports. AEs are defined as any unexpected medical problem that happens during the observational window after application of the study drug regardless of whether it is a side effect of the study drug or not. SAEs are defined as any adverse event that results in death, causes a life-threatening situation or initiates or prolongs hospitalization, causes disability or permanent damage or requires intervention to prevent permanent impairment or damage. If a SAE was present, this was reported to the sponsor´s representative within 24 hours. In case a SAE would not have been resolved within the 14th postoperative day, the sponsor's representative would initiate further follow-up of any possible related events and a follow-up investigation after 3 months. All events were reported to the Federal Institute for Drugs and Medical Devices in Germany.

2.8 Statistics

After the safety documentation and documentation of possible protocol violations of the last patient was complete (last patient, last visit), the data were unblinded. Data were only transferred to the database after careful plausibility check by the clinical research physician and approval by the assigned monitor of the study. After completion of the database a double check was performed by a second independent assessor.

Statistical analysis of the primary endpoint was performed with the Fischer-Boschloo test because this test has greater statistical power than the Fischer´s Exact test while enabling the same level of type 1 error. Statistical significance was defined by a two-sided alpha of 5%. For the primary endpoint the statistical program R 4.1.2 was used as the Fischer-Boschloo Test is not available in IBM® SPSS 25. For all other statistical calculations IBM® SPSS 25 was used.

Analysis of baseline characteristics as possible confounding factors was done by determining its statistical significance using a Chi-square Test for nominal data and Mann-Whitney-U Test for ordinal data. Means and standard deviations of baseline characteristics were calculated by using an independent sample T-test.

2.9 Comparison to the most recent RCTs

To compare the results of our study to the most recent RCTs published on the intra- and postoperative administration of dexmedetomidine, the following PUBMED search was used: "(Dexmedetomidine OR Dexdor) AND (Delirium OR delirious) AND (peri-operative OR

perioperative OR intraoperative OR intra-operative)". Furthermore cross-references of the latest meta-analyses and RCTs were checked to screen for additional studies.

3. Results

We assessed 484 patients for eligibility between July 2014 and July 2018 of which 63 were enrolled and 60 were analysed on an intention-to-treat basis. The selection process is displayed in the study flow diagram of figure 3. The 253 patients that had to be excluded because of other reasons were mainly of logistical origin: it happened more often that two patients were eligible but scheduled at the same day around the same time. Also, patients could not be included when informed consent could not be obtained timely, prior to apothecary closing hours. Moreover, sometimes the patient was not available at the time of screening (e.g. because the patient was undergoing additional studies). Finally, it could happen that the research physician or research assistants were not available on the day an eligible patient was scheduled for surgery.
Baseline characteristics of the patients can be found in table 1.

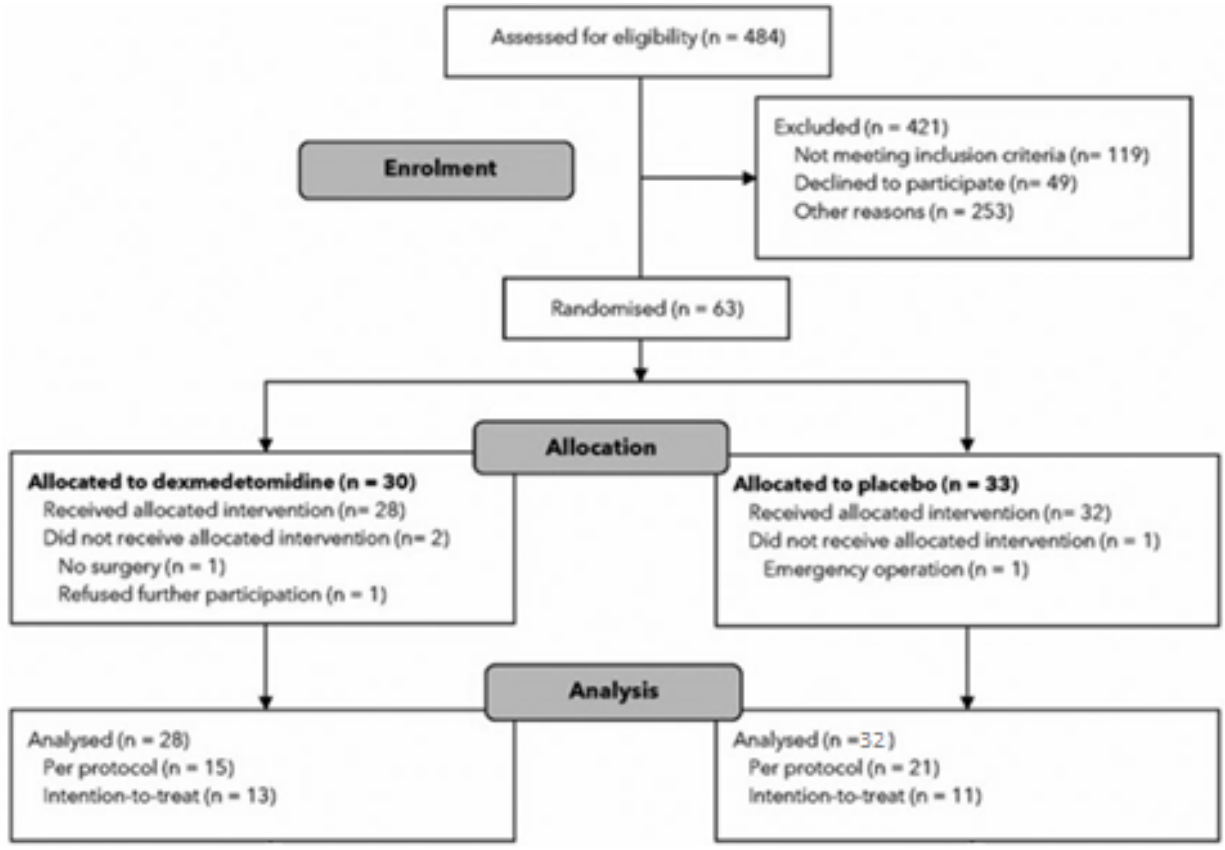

Figure 3: Study flow diagram for delirium assessment, modified to van Norden et al.[13]

Table 1: baseline characteristics, authors own table, authors own depiction

Baseline characteristics of the 60 patients included according to intention-to-treat analysis

	Dexmedetomidine (n=28)	*Placebo (n=32)*	*P-value*
Age; years, mean (SD)	70.43(7.14)	70.5 (6.23)	0.882
Female; n (%)	9(32.2)	9(28.1)	0.735
BMI; kg.m^{-2}, mean (SD)	26.97 (4.93)	28.03 (4.66)	0.505
Site of surgery; n (%)			
Pancreatic	13 (46.4)	16 (50.0)	
Surgery	9 (32.1)	8 (25.0)	0.823
intra-abdominal other than pancreatic surgery	6 (21.4)	8 (25.0)	
Cardiac			
ASA Status, n (%)			
1 or 2	14 (50.0)	16 (50.0)	0.636
3 or 4	14 (50.0)	16 (50.0)	
β -blocker yes, n (%)	15 (52.6)	18 (56.3)	0.835

SD = standard deviation, n = number of patients

As can be seen, no significant differences were found between the baseline characteristics of the two groups. Most patients were male and approximately 70 years old. The main type of surgery in our study was pancreatic surgery. There were 3 drop-outs: one patient was unexpectedly scheduled for emergency surgery, prior to the originally planned surgery and therefore had to be excluded. Furthermore, 2 other patients withdrew informed consent: one withdrew shortly after giving informed consent, prior to surgery and a second patient, undergoing cardiac surgery, withdrew postoperatively. In total, 28 Patients were randomized in the dexmedetomidine group and 32 in

the placebo group. Of these patients, 46 underwent major abdominal surgery and 14 underwent CABG-surgery (See table 1).

36 Patients (60%) were treated according to study protocol and in 24 patients protocol violations were reported. Major protocol violations concerned randomization in the wrong treatment group, variation in the length of dexmedetomidine administration and subsequent occurrence of an exclusion or violation of an inclusion criterion. The occurrence of protocol violations was compared between the two groups and did not lead to any significant differences between the two groups.

Our study showed a significant reduction of POD from 43.8% in the placebo group to 17.9% in the dexmedetomidine group. The relative risk ratio (RR) for POD in the dexmedetomidine group was 0.41. Analysis of the β -blocker strata did not reveal any statistically significant differences: the reduction of POD in the β-blocker therapy stratum was 56% to 20% (p=0.0504) and 29% to 15% in the stratum without β-blocker therapy (p=0.5632).

Amongst patients undergoing cardiac surgery 3 (21.4%) patients in the dexmedetomidine group and 6 (42.9%) in the placebo group developed a POD (p=0.049). Within the group of patients undergoing abdominal surgery 2 (4.3%) patients in the dexmedetomidine group and 8 patients (17.4%) in the placebo group developed a POD (p=0.057).

The bar graph in figure 4 displays the number of patients developing a POD in the dexmedetomidine and placebo group for both cardiac and non-cardiac surgery patients. The bar graphs of figure 5 to 8 then further differentiate into the β-blocker strata and into the individual intra-abdominal and cardiac surgery strata.

With regards to safety, the incidence of bradycardia reported in the dexmedetomidine (20 patients (33.9%) was comparable to that of the placebo group (21 patients (35.6%). Of the 324 reported AEs, 44 were noted as possibly related to the study drug: 22 patients in both the dexmedetomidine and placebo group (6.8% vs 6.8%) and therefore the difference was not statistically significant. In total 18 SAEs were reported, of which the difference between the dexmedetomidine group (n=8, 44.4%) and placebo group (n=10, 55.6%) was not statistically significant (p=0.871).

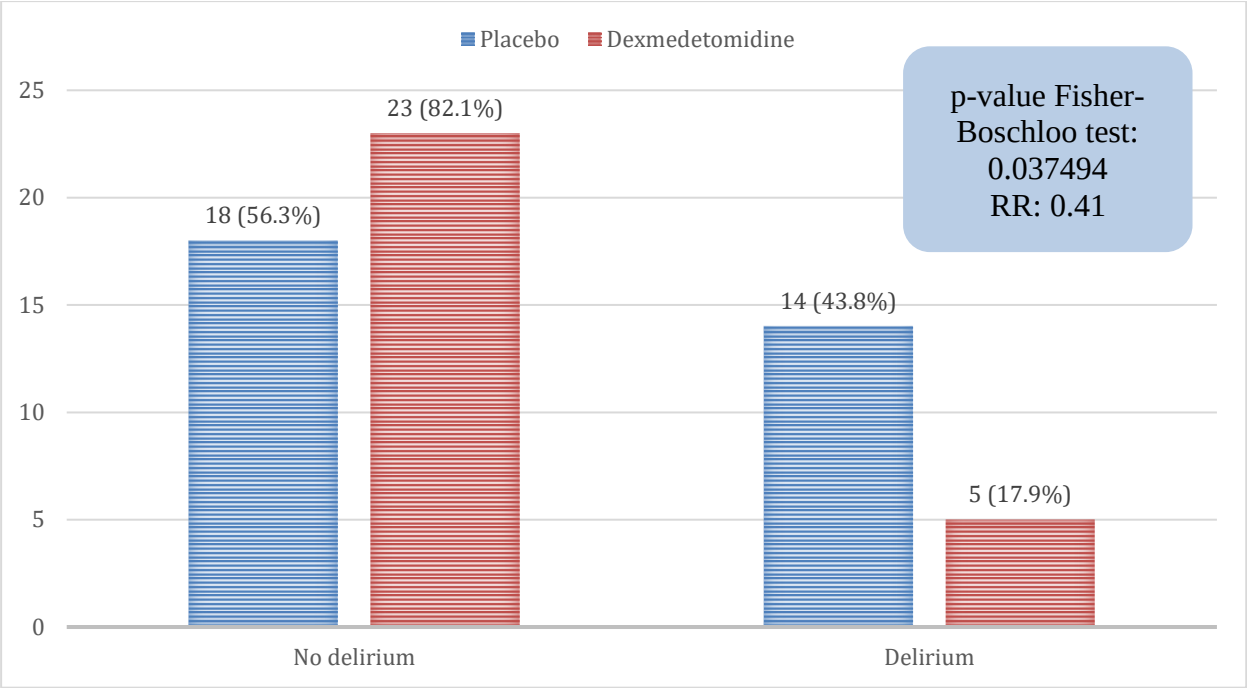

Figure 4: Number and rate of patients with postoperative delirium, authors own depiction
RR = Relative Risk

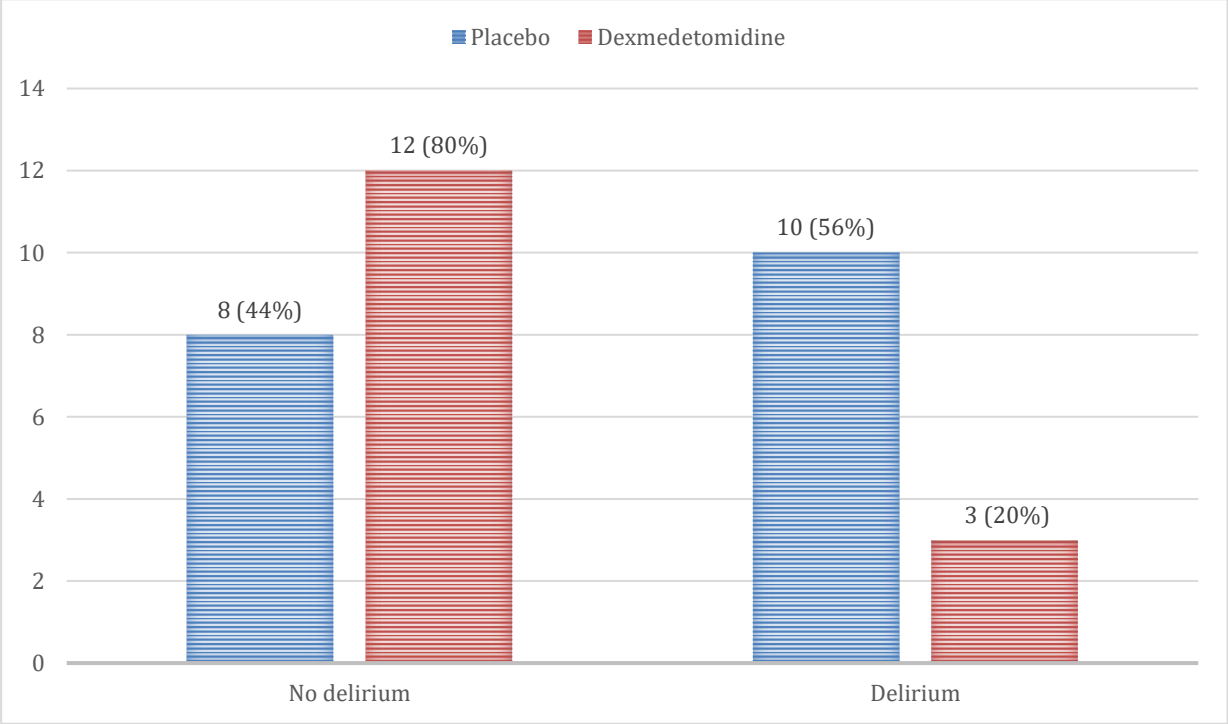

Figure 5: Number and rate of postoperative delirium in patients receiving beta-blocker therapy, authors own depiction

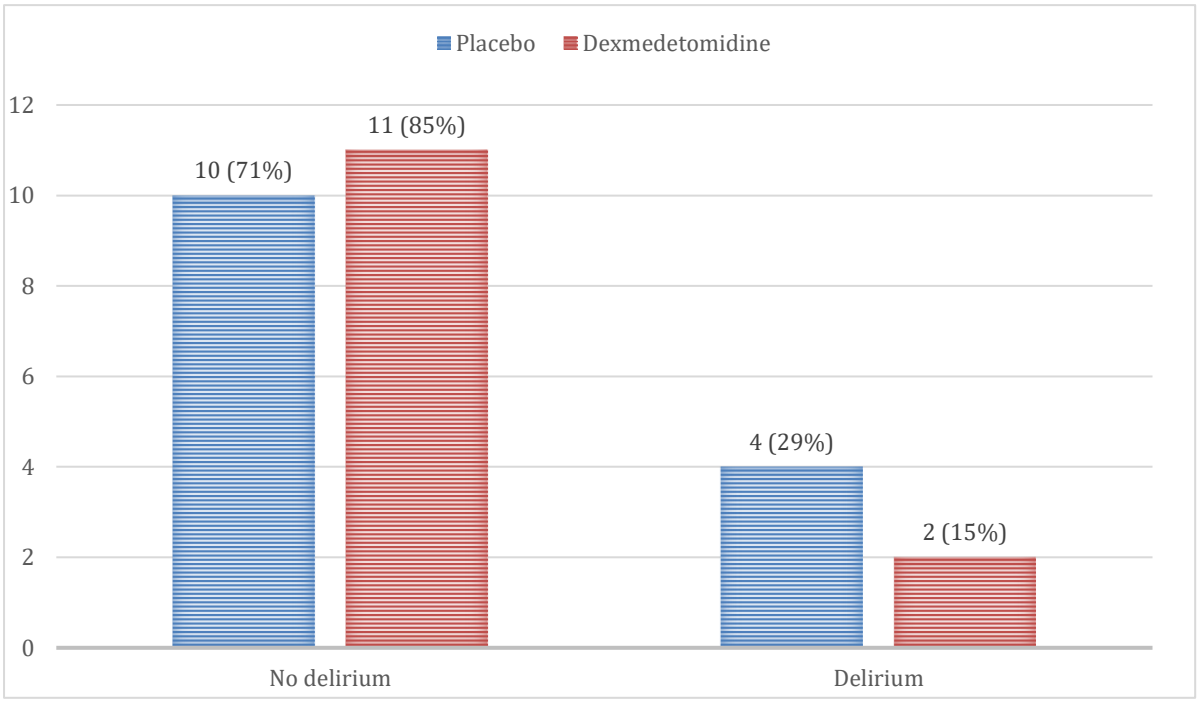

Figure 6: Number and rate of postoperative delirium in patients without beta-blocker therapy, authors own depiction

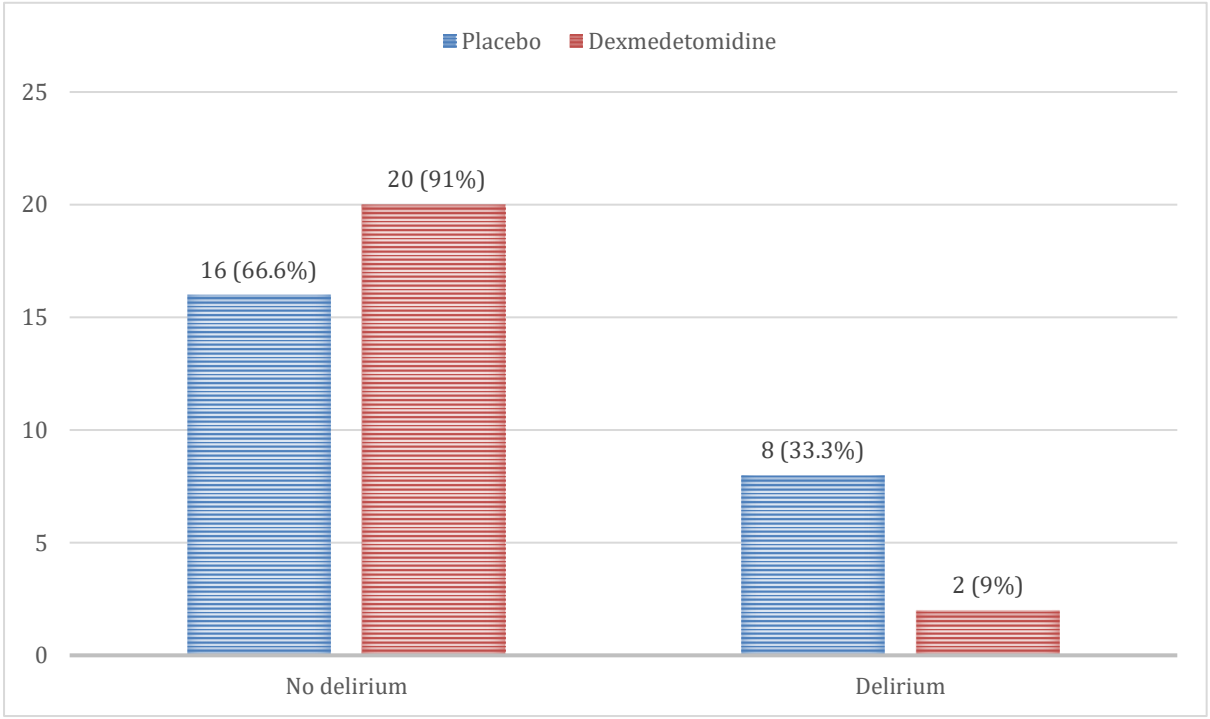

Figure 7: Number and rate of postoperative delirium in patients receiving major abdominal surgery, authors own depiction

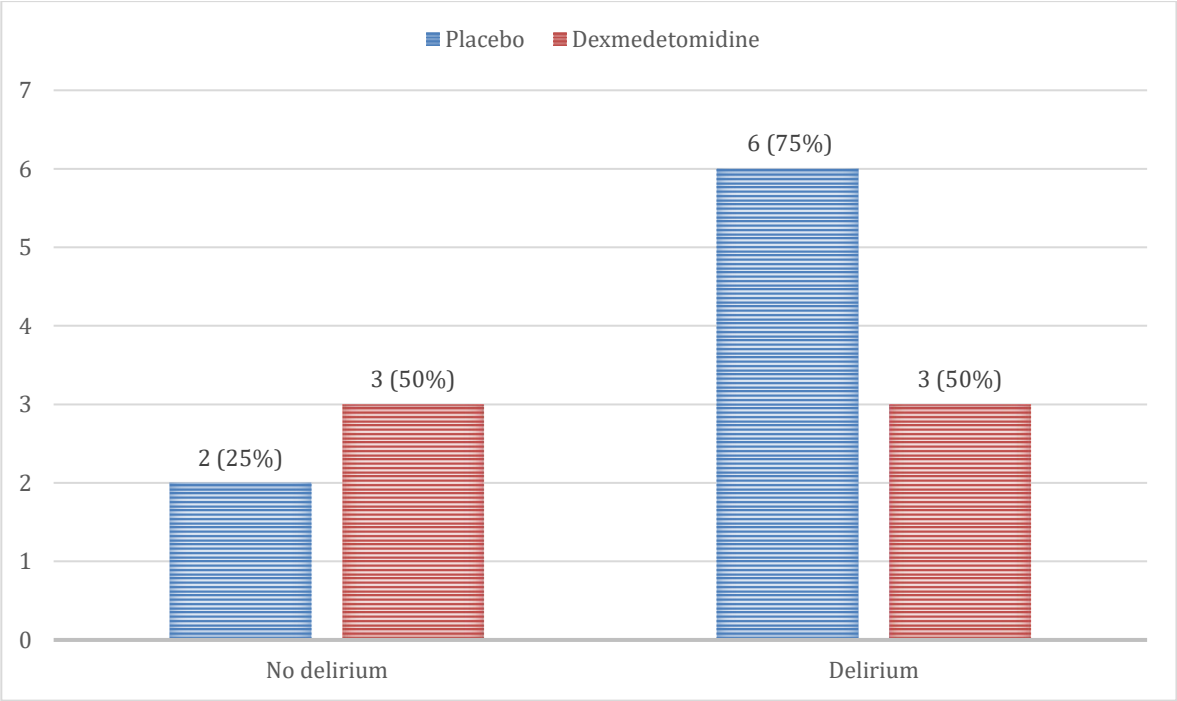

Figure 8: Number and rate of postoperative delirium in patients undergoing cardiac surgery, authors own depiction

4. Discussion

4.1 Summary of the results

Amongst elderly (≥60 years) patients and high-risk surgeries with a foreseeable longer stay on the ICU our trial found a significant reduction of POD of 44% in the placebo group to 18% in the dexmedetomidine group for all patients. Furthermore, the safety analysis showed a comparable incidence of AEs and SAEs in both the dexmedetomidine and placebo group. Except for the cardiac surgery stratum, no statistically significant difference in in POD incidence was found amongst the other strata (β-blocker, no-β-blocker and non-cardiac surgery).

4.2 Further interpretation of the results

Interestingly, although without statistical significance, the highest reduction of POD in our study, amongst al subgroups, was found in patients receiving β-blocker therapy (56% to 20%). A possible explanation might lie in the lower and stabler heart rate, found amongst patients with a combination of β-blocker therapy and dexmedetomidine: a recent study by Singh et al. done amongst CABG-surgery patients looked at the sympathomimetic response during laryngoscopy and intubation [57]. Patients were randomized into 3 subgroups (all n=30): a group that received

an additional combination of dexmedetomidine and esmolol (DE) during induction and two other subgroups that received either dexmedetomdine (D) or esmolol (E). They found a significantly lower and stabler heart rate in the combination group during all time intervals (from study drug infusion until 5 minutes after intubation) compared to the other two groups. A higher heart rate means increased metabolic demand. This can already be a limiting factor for coronary blood flow in patients with stenoses of moderate severity [58] and can therefore result in myocardial ischemia and reduction in cardiac output and might explain why the reduction in POD is greater in patients that are on β-blocker therapy. Furthermore, as mentioned earlier, stimulation of the β1-receptor increases intracellular cAMP which can induce a reduction of inflammatory cytokines like TNF-α and IL-1β and can increase anti-inflammatory cytokines like IL-10. [50, 51].

4.3 Strengths and limitations of our study

The major limitation of our study was a relatively small sample size, in comparison to many other RCTs. This was especially the case in cardiac surgery patient stratum (n=14), despite the finding of a significant reduction POD incidence in the dexmedetomidine group for this stratum, as the study was not statistically powered for this subgroup only. This greatly limits its generalizability of the study for cardiac surgery patients. Nevertheless our study has incorporated several aspects that are very important with respect to a methodologically sound RCT that investigates the intraoperative use of dexmedetomidine: the use of the goldstandard screening tool CAM/CAM-ICU, preselection of age, use of neuromonitoring and focus on high-risk surgeries with a foreseeable longer stay on the ICU.

Preselection of age is important as the highest incidence of delirium and therefore the maximal potential of dexmedetomidine can be found amongst people of 60 years and older, further increasing with the progression of age, especially in patients with pre-existing cognitive impairments [16]. Furthermore, dexmedetomidine is a co-sedative and has sparing properties on prodelirogenic drugs like hypnotics and opiates. Therefore, the use of neuromonitoring is important to avoid oversedation or even burst-suppression (which can be observed as the absence of EEG-waves during neuromonitoring as a consequence of oversedation). This is especially important in patients from the verum group, as the cosedative effects of dexmedetomidine harbours the risk of oversedation.

Finally, a focus on major surgeries with a foreseeable longer stay on the ICU is important as these are surgeries that can yield the highest rates of POD. The bigger the surgery, the more pro-inflammatory cytokines will be released systemically and cross the blood brain barrier, and

therefore the more microglial cells will be activated, increasing the risk for POD. If these aspects are not factored in, this might negate the effects of intraoperatively administered dexmedetomidine. Mainly looking at an RCTs sample size without looking at these aspects might therefore be misleading.

4.4 Results in light of the literature

So far, quite a few meta-analyses have been done looking at the perioperative administration of dexmedetomidine for the prevention of POD [59-66] of which the meta-analysis of Lin et al. was the latest. They looked at studies amongst cardiac- as well as non-cardiac surgery patients and identified 11 trials in which dexmedetomidine was given perioperatively (9 intra- and 2 intra- and postoperatively) in which our trial was not yet included. One RCT however (Cheng et al. Anesthesia 2019) had to be retracted by the publisher because of inauthentic data[67]. In recent years, especially since 2018, the body of evidence regarding the perioperative administration of dexmedetomidine for delirium prophylaxis has grown substantially. After checking cross-references of meta-analyses and RCTs, taking out the retracted study and doing a thorough search on PUBMED 16 non-cardiac and 6 cardiac RCTs were identified that focused on the intraoperative administration of dexmedetomidine for the prevention of POD. This amounts to 10 additional non-cardiac and 3 additional cardiac RCTs that were published after our article and that were not yet reviewed in our discussion at the time. In the following reviews, these new articles will be discussed. An overview of all the articles can be found in tables 2 and 3.

Table 2: Overview of studies in non-cardiac surgery, authors own depiction

RCTs on intraoperative dexmedetomidine administration for the prevention of POD in non-cardiac surgery patients

Study	Total number of patients (n=) / Age (years)	Operation Type	Bolus and/or infusion rate of dexmedetomine	Rate of POD (Dex versus placebo (unless stated otherwise))	Limitations
Van Norden et al. 2021 [13]	60 (≥60)	Major cardiac / non-cardiac	0.7 $\mu g \cdot kg^{-1} \cdot h^{-1}$	17.9% vs. 43.8% (p = 0.04)	Small sample size
Zhang et al. 2020 [35]	240 (≥65)	Hip fracture surgery	0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$	18.2% vs. 30.6 (p = 0.03)	No neuromonitoring
Li et al. 2020 [22]	619 (≥60)	Intrathoracic/abdominal/spinal	0.6 $\mu g \cdot kg^{-1}$ + 0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$	5.5% vs. 10.3% (p = 0.03)	Dex stopped 1 h before end of surgery
Xin et al. 2020 [34]	60 patients with MCI (≥65)	Laparoscopic cholecystectomy	0.5 $\mu g \cdot kg^{-1}$ + 0.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$	10% vs. 33.3% (p = 0.03)	-Dex stopped 30 min before end of surgery -Small sample size -No neuromonitoring
Kim et al. 2019 [68]	120 (18-75)	Thoracosopic lung resection	0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$	25% vs. 25% (p = 1.00)	-No neuromonitoring -No focus on elderly patients
Mei et al. 2018 [69]	296 (≥65)	Hip arthroplasty (under regional anesthesia)	0.8-1.0 $\mu g \cdot kg^{-1}$ + 0.1-0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$	7% vs. 16% (p = 0.03)	No neuromonitoring
Lee et al. 2018 [43]	318 (≥65)	Laparoscopic surgery	1 $\mu g \cdot kg^{-1}$ +0.2-0.7 $\mu g \cdot kg^{-1} \cdot h^{-1}$	9.5% vs. 18.4% (Bolus only) vs. 24.8% (placebo) (p < 0.017)	No fixed rate of dexmedetomidine. Titration based on hemodynamic changes.
Huyan et al. 2018 [70]	173 (≥65)	Lung cancer surgery	0.5 $\mu g \cdot kg^{-1}$ + 0.1 $\mu g \cdot kg^{-1} \cdot h^{-1}$	Significant reduction in dexmedetomidine group on	-No CAM-ICU but ICDSC

				postoperative day 1-5 (No raw data available)	-Dex stopped 30 min before surgery
He et al. 2018 [24]	90 (75-90)	Orthopaedic surgery	0.5 $\mu g \cdot kg^{-1}$ + 0.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$	Significant reduction in dexmedetomdine group on postoperative day 1-5 (No raw data available)	Small sample size
Tang et al. 2018 [26]	120 (18-70)	Intracranial aneurysm embolization	1 $\mu g \cdot kg^{-1}$ + 0.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$	15% vs. 23% (p = 0.038)	-No focus on elderly patients
Deiner et al. 2017 [71]	390 (≥68)	Thoracic, orthopaedic, urologic, spine	0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$	11.8% vs. 12.2% (p = 0.94)	-Major Surgery only defined as hospitalisation of at least 2 days -No neuromonitoring
Yu et al. 2017 [72]	92 (≥60)	Thoracic surgery	0.2-0.7 $\mu g \cdot kg^{-1} \cdot h^{-1}$	6.5% vs. 21.7% (Dex vs. Midazolam) (p < 0.05)	-Timing of administration not properly described -Small sample size -No neuromonitoring
Liu et al. 2016 [16]	197 (≥65) (subanalysis 65-75 and >75 between aMCI and non-aMCI patients)	Hip/knee/shoulder surgery	0.2-0.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$	aMCI group: -65-75 years: 22.6% vs. 43.3% (p < 0.01) →75 years: 37.5 vs. 90% (p < 0.01) Non-aMCI group: -65-75 years: 11.9% vs. 30.8% (p < 0.01) →75 years: 16.7% vs. 36.8% (p < 0.01)	No neuromonitoring
Naik et al. 2016 [23]	131 (18-80)	thoracic and/or lumbar spine surgery	1 $\mu g \cdot kg^{-1}$ + 0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$	1.6% vs. 4.5% (p = 0.62)	No focus on elderly patients

Yang et al. 2015 [73]	79 (18-80)	Free flap surgery	0.5 µg·kg^{-1} +0.2-0.7 µg·kg^{-1}·h^{-1}	5.1% vs 12.5% (p = 0.43)	-Small sample size -No focus on elderly patients -No neuromonitoring
Ma et al. 2013 [74]	90 (≥60)	Orthopaedic surgery	1 µg·kg^{-1} + 0.5 µg·kg^{-1}·h^{-1}	6.7% vs 26.7% (p < 0.05) (Ketamine + dex vs. Ketamine only)	-Original article not available in English -Small sample size -No neuromonitoring

aMCI = amnestic mild cognitive impairment. n = number of patients. h = hour. min = minutes. vs. = versus. MCI = mild cognitive impairment. Dex = dexmedetomidine. In some studies p-values for the incidence of POD cannot be reported because raw data was not offered in the paper.

Table 3: Overview of studies in cardiac surgery, authors own depiction

RCTs on intraoperative dexmedetomidine administration for the prevention of POD in cardiac surgery patients

Study	**Total number of patients (n=) / Age (years)**	**Operation Type**	**Bolus and/or infusion rate of dexmedetomine**	**Rate of POD (Dex versus placebo)**	**Limitations**
Likhvantsev et al. 2021 [75]	169 (>45)	CABG and/or valve replacement	0.7 µg·kg^{-1}·h^{-1} (intraoperative) 0.4 µg·kg^{-1}·h^{-1} (ICU)	7.1% vs. 18.8% (p = 0.02)	-No focus on elderly patients -No neuromonitoring
Turan et al. 2020 [46]	794 (18-85)	CABG-surgery	0.1-0.4 µg·kg^{-1}·h^{-1} (intraoperatively)	17% vs. 12% (p > 0.05)	-No focus on elderly patients -No neuromonitoring
Shi et al. 2019 [47]	164 (>66)	CABG and/or valve replacement and replacement of ascending aorta	0.4-0.6 µg·kg^{-1}·h^{-1}	39.3% vs. 26.35% (p = 0.08)	-No neuromonitoring -Timing of administration not properly described

Massoumi et al. 2019 [76]	88 (40-80)	CABG-surgery	1 μg·kg^{-1} + 0.2-0.7 μg·kg^{-1}·h^{-1}	9.1% vs. 20.5% (p = 0.04)	-Small sample size -No focus on elderly patients -No description of delirium assessment method -Timing of administration not properly described
Sheikh et al. 2018 [77]	60 (15-60)	Elective open heart surgery	1 μg·kg^{-1} + 0.2-0.6 μg·kg^{-1}·h^{-1}	3.3% vs. 23.3% (p = 0.02)	-Small sample size -No focus on elderly patients -No delirium detection tool used -Timing of administration not properly described -No neuromonitoring
Li et al. 2017 [78]	285 (≥60)	CABG and/or valve replacement	0.4-0.6 μg·kg^{-1}·h^{-1}	4.9% vs.7.7% (p = 0.34)	No neuromonitoring

CABG = coronary artery bypass graft. n = number of patients. Dex = dexmedetomidine. h = hour. vs. = versus.

4.4.1 Review of non-cardiac RCTs

The majority of non-cardiac studies (13 out of 16, see table 1) showed a significant reduction in the incidence of POD in the dexmedetomidine group. Timing and dosage of dexmedetomidine administration, with or without prior bolus, varied widely between studies. Five studies included more than 200 patients. The biggest and one of the newest studies amongst them was done by Li et al. (2020), who included 619 patients of 60 years and older[22]. They were scheduled for major surgery (intrathoracic, abdominal or spinal surgery expected to last more than 2 hours) and randomized into a dexmedetomidine (n=309) and placebo group (n=310). Patients were administered a loading dose of 0.6 μg·kg^{-1} given 10 minutes prior to induction, followed by a continuous infusion of 0.5 μg·kg^{-1}·h^{-1} until the end of surgery. POD was monitored twice daily by CAM until POD 5, and BIS was used as neuromonitoring with a target range of 40-60. CAM testing physicians were trained by psychiatrists before the study begun and after 4- and 6-months intervals - including simulation training courses with patient-actors. A significant reduction was found in POD from 10.3% (n=32) in the placebo group to 5.5% (n=17) in the dexmedetomidine

group. Moreover, a significant reduction in non-delirium complications (26.1% to 19.4%) was found, in particular surgery-related complications such as gastro-intestinal bleeding and sepsis.

Zhang et al.[35] randomized 240 patients of 65 years and older, scheduled for hip arthroplasty, into a dexmedetomidine (n=120) and intervention group (n=120). CAM was used to screen for POD once daily and this study was the first to look at the effects of perioperative administration of dexmedetomidine on inflammatory markers such as TNF-α, IL-1 β and IL-6. They found that, when administering patients 0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ 30 minutes before the start of induction, which was then adjusted to 0.3 $\mu g \cdot kg^{-1} \cdot h^{-1}$ intraoperatively, the incidence of POD could be significantly reduced from 30.6% to 18.2% (p=0.03). And just like in the study of Xin et al. [34]which came out less than a year later, they were able to show a significant reduction in postoperative levels of TNF-α by dexmedetomidine, which was measured at the time of suture as well as 30 min postoperatively (in the study of Xin et al. they found a significant reduction was found on the second and third postoperative day). This confirms that dexmedetomidine is indeed able to downregulate the concentration of TNF-α as earlier found in animal studies, when a systemic inflammatory trigger such as surgery is present [21,30].

Including our own study, there were 11 other smaller non-cardiac RCTs (n<200). Of these three are interesting to highlight: two studies that offer insight in the prophylactic potential of dexmedetomidine with regards to radical versus minimally-invasive surgery and a third study that did a subgroup analysis on patients with mild cognitive impairment. Huyan et al., randomized 173 patients of 65 years and older, undergoing radical pulmonary resection as treatment for lung cancer, into a dexmedetomidine (n=173) and placebo group (n=173)[70]. Twenty Minutes before the start of surgery patients in the intervention group were given a loading dose of 0.5 $\mu g \cdot kg^{-1}$ followed by a continuous low-dose infusion of 0.1 $\mu g \cdot kg^{-1} \cdot h^{-1}$ until 30 minutes before the end of surgery. POD was assessed once daily by ICDSC for the first 7 postoperative days and neuromonitoring was used with a BIS-target range of 40-60. In the results they mention a significant reduction in the intervention group for POD 1-5, displaying this in a figure although raw data was not offered. Their study suggests that even a low-dose strategy in these patients might be effective.

Another non-cardiac RCT by Kim et al. (n=120, patients aged 18 to 75 years) [68] looked at minimally invasive thoracoscopic lung cancer surgery (video-assisted thoracoscopic lobectomy/segmentectomy) They did not find a reduction in the incidence of POD but as their

study lacked a focus on elderly patients and only looked at minimally invasive thoracoscopic surgery the absence of this preselection might have negated the effects of dexmedetomidine.

Liu et al. performed an interesting study that not only randomized patients, but also did a subgroup analysis on mild cognitively impaired patients[16]. This was the first study so far to do this. They randomized 197 orthopaedic patients (hip, knee and shoulder surgery) of 65 years and older into a group with amnestic mild cognitive impairment (aMCI) (n=59) and a group without (n=118). Two subgroups from both groups were randomized into a dexmedetomidine and placebo group: an aMCI DEX group (n=39), an aMCI placebo group (n=40), a non-aMCI DEX group (n=60) and a non-aMCI control group (n=58). Moreover, these groups were then stratified into two age categories (65-75 years and 75 years and older) to investigate the correlation between age and POD incidence. Patients were administered an infusion rate from 0.2-0.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$ shortly after induction of anesthesia and stopped 20 minutes before the expected end of surgery. CAM was used to screen for delirium, however only once daily on postoperative day 1, 3 and 7. No neuromonitoring was used. For both aMCI and non-aMCI groups a significant reduction of POD was found compared with their respective placebo groups. Furthermore, they found that in the aMCI control group, there was a linear correlation between age and the incidence of POD. In addition, incidences of POD were significantly higher in the aMCI control group in comparison to the non-aMCI control group and the reduction of POD by dexmedetomidine was the greatest in the aMCI >75 years subgroup (90% in the placebo vs. 37.5% in the dexmedetomidine group). These results suggest that the incidence of POD increases with the progression of age and that especially elderly patients with aMCI seem to be susceptible for the development of delirium. A later study, done by Xin et al. also found an almost threefold reduction of POD by intraoperatively administered dexmedetomidine amongst patients with mild cognitively impairment[34].

The remaining 8 smaller non-cardiac RCTs varied in study group size around 100 patients (n 60-131). Of all RCTs our study[13] was the only one to look at both non-cardiac and cardiac surgery patients. One study performed in orthopaedic surgery patients older than 60 years randomized patients into a ketamine + dexmedetomidine (n=30), ketamine (n=30) and a control group (n=30)[74]. Patients in the first group were given an additional bolus of dexmedetomidine of 1 $\mu g \cdot kg^{-1}$ 10 minutes prior to induction, followed by a continuous infusion of dexmedetomidine of 0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ until 30 minutes before the end of surgery. POD was assessed once daily by CAM at 1 hour postoperatively, and on postoperative day 1 and 3. No neuromonitoring was done. They found a significant reduction in POD in the ketamine + dexmedetomidine group (0% (n=0)) in

comparison to the ketamine only group (26.7% (n=8)). They therefore argue that dexmedetomidine might be able to alleviate the side effects of ketamine. Further details on the remaining non-cardiac RCTs can be found in table 2.

4.4.2 Review of cardiac RCTs

In total, there were 6 non-cardiac RCTs that also focused on intraoperative administration of dexmedetomidine. Of these, by far the biggest cardiac RCT - and RCT in general - was the DECADE trial, a multi-center RCT done by Turan et al[46]. They analysed 794 patients of 18-85 years, undergoing CABG-surgery into a dexmedetomidine (n=397) and a placebo group (n=395). POD was assessed by CAM-ICU twice daily and by additional chart review. No neuromonitoring was done. Patients in the dexmedetomidine group received 0.1 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ from the time of incision, followed by an increase to 0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ at the end of bypass. Postoperatively, the dose was increased to 0.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$ which was then continued for 24 hours. The trial was terminated per protocol after futility boundaries were reached. POD was found in 17% of patients (n=67) in the dexmedetomidine group and 12% of patients in the placebo group (n=46) (no statistical significance). The authors state, that this might also partially be explained by the higher incidence of clinically important hypotension in the dexmedetomidine group of 57% versus 36% in the placebo group, which might explain the higher incidence of delirium, found in this group as well. Moreover, a possible dexmedetomidine induced hypotension could be worsened by the already profound atherosclerotic vascular status. Although coronary autoregulation is able to preserve myocardial perfusion in stenoses of moderate severity, increased metabolic demand can be a limiting factor for coronary blood flow [78]. This then might worsen the already existing hypotension by means of myocardial ischaemia and reduction of cardiac output. They state that dexmedetomidine infusion did not reduce delirium in patients recovering from cardiac surgery and that it should not be infused in these patients.

However, there were some major methodological issues in this study which might have negated the effect of dexmedetomidine. The intraoperative dose of dexmedetomidine might have been subtherapeutic as most RCTs published so far use higher doses. No preselection of age took place. Furthermore, no definition of clinically important hypotension was given. As the safety meta-analysis of Wang et al. [45] (18 RCTs, 1730 patients with mainly postoperative administration of dexmedetomidine) did not find a higher incidence of hypotension by dexmedetomidine, it is not unlikely that other mechanisms might be at play. This should have been addressed and further evaluated in the article. Finally, no neuromonitoring was used.

Likhantsev et al. analysed 169 patients of 45 years and older undergoing CABG and/or valve surgery[75]. They were randomized into a dexmedetomidine (n=84) and placebo group (n=85). Patients received a continuous administration of dexmedetomidine of 0.7 $\mu g \cdot kg^{-1} \cdot h^{-1}$, starting from the time of induction which was then adjusted to 0.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$ upon arrival on the ICU. POD was tested by CAM-ICU twice daily and was also assessed by ICDSC as secondary endpoint. No neuromonitoring was used. They found a significant reduction of POD in the dexmedetomidine group from 18.8% (n=16) to 7.1% (n=6) in the placebo group (n=0.02). Moreover, a slight but significant reduction in ICU and hospital length of stay was observed. The authors state that a crucial point in their study for the prevention of POD might have been the starting timing of dexmedetomidine prior to cardiopulmonary bypass because its action might be mediated by preconditioning properties[79]. At this point only 6 cardiac RCTs have been done, of which only three have properly described the starting timing of dexmedetomidine [46,75,78]. All of these started dexmedetomidine at induction and therefore prior to cardiopulmonary bypass. Therefore, further studies will be needed to elucidate this standpoint.

Shi et al. analysed 164 patients of 60 years and older undergoing various types of cardiac surgery but mainly CABG-surgery (65%) [47]. Patients were given a continuous intraoperative infusion of dexmedetomidine of 0.4-0.6 $\mu g \cdot kg^{-1} \cdot h^{-1}$ although exact timing was not properly described. Like Turan et al. they also found a non-significantly increased risk of POD amongst patients in the dexmedetomidine group ((39.3%), n=33) in comparison to the placebo group ((26.3%), n=21), p=0.08).

So far, the evidence for the intraoperative administration of dexmedetomidine in cardiac patients for the prevention of POD remains controversial. Turan et al. and Shi et al., two of the bigger cardiac RCTs found a non-significantly increased incidence of POD in the dexmedetomidine groups[46,47]. However, the low-dose strategy used by Turan et al. might have been subtherapeutic. Only 2 out of 6 cardiac RCTs focused on elderly patients - in contrast with 12 out of 16 in non-cardiac RCTs - and only 1 study used neuromonitoring. Li et al. (2017) found an unexpected low incidence of POD in both the dexmedetomidine and placebo group, therefore not being able to find an effect of intraoperatively administered dexmedetomidine[78]. Likhantsev et al. was the only bigger RCT that found a significant reduction in POD amongst cardiac patients together with the two smaller sized and lower quality RCTs of Massoumi et al. and Sheikh et

al.[75–77]. Therefore, further methodologically sound cardiac RCTs that focus on elderly patients are needed to shed a brighter light on the efficacy and safety of dexmedetomidine in these patients.

4.5 Clinical use for our daily practice

Current studies indicate that a bolus-only strategy is most likely not sufficient and that different dosing strategies, varying from 0.1-0.7 $\mu g \cdot kg^{-1} \cdot h^{-1}$ with or without bolus, have shown to be successful in the prevention of POD. Our study [13] indicates that the perioperative administration of dexmedetomidine in non-cardiac patients seems to be safe, not in the least because of the perioperatively carefully monitored setting of the operating room and ICU. Considering the high and incremental mortality rate resulting from each day with a delirium, the benefits of intraoperative administration of dexmedetomidine in non-cardiac surgery patients could outweigh the risks. In our university hospital high-risk intrathoracic or intra-abdominal invasive surgeries amongst elderly patients are done on a daily basis. A multitude of physiological derangements like intraoperative volume-shifts and metabolic disorders, release of pro-inflammatory cytokines, pre-existent mild cognitive impairment together with age above 65 years and other predisposing factors make these patients especially prone to develop a POD. Therefore, as shown by numerous RCTs, when carefully selected for age and scope of surgery and when neuromonitored to prevent oversedation, the use of dexmedetomidine could reduce the rate of POD in non-cardiac patients and could therefore reduce postoperative mortality as well. An new meta-analysis regarding both the intra- and postoperative prophylactic use of dexmedetomidine in non-cardiac surgery patients would provide a better answer, which then could be incorporated into the newest guidelines.

5. Conclusion

The current body of evidence regarding the intraoperative administration of dexmedetomidine for neuroprotection is indicative of a significant reduction in POD for non-cardiac surgery patients as 13 out of 16 non-cardiac surgery with intraoperatively administered dexmedetomidine found a significant reduction of POD. Our trial found a significant reduction of POD from 43.8% to 17.9%. and was the first to look at the clinical implications of intra- and postoperative administration of dexmedetomidine in both non-cardiac and cardiac high-risk patients. If the intraoperative administration of dexmedetomidine is tailored to the age and scope of surgery and oversedation by neuromonitoring is carefully avoided, it could yield a significant reduction in POD amongst non-cardiac surgery patients. To this regard, a newer meta-analysis including these latest studies is needed to give a better answer. Also, a sedation-only strategy as adjunct to regional

anesthesia seems to be a promising modality [69]. By now, a case for the intraoperative use of dexmedetomidine in elderly non-cardiac patients undergoing high-risk surgeries has been made, especially in the eldest patients (>75 years) with or without the presence of aMCI [16]. Preselection of age, high-risk surgeries with a foreseeable longer stay on the ICU and the use of neuromonitoring are important elements to optimize effectivity of dexmedetomidine. Although 3 out of 6 cardiac surgery RCTs found a significant reduction POD after intraoperatively administered dexmedetomidine, 2 of these were of poor methodological quality. Moreover, the RCTs of Turan et al. and Shi et al. have cast some doubt on the safety of the intraoperative use of dexmedetomdine in cardiac patients[46,47]. Therefore, further methodologically sound studies for cardiac surgery patients are needed to properly evaluate its efficacy and safety as a preventive modality.

6. References

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7. Eidesstattliche Versicherung

„Ich, Jeroen Rieske, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: ´Delirprävention bei älteren Patienten durch intraoperative Gabe von Dexmedetomidin bei Hochrisikoeingriffen/ Prevention of delirium by intraoperative administration of Dexmedetomidine to elderly patients during high-risk surgery´ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Erstbetreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum 12.12.2022 Unterschrift

8. Anteilserklärung an den erfolgten Publikationen

Jeroen Rieske hatte folgenden Anteil an der folgenden Publikation, in die die Ergebnisse seiner Dissertation eingeflossen sind:

van Norden J., Spies C.D., Borchers F., Mertens M., Kurth J., Heidgen J., Pohrt A. & Mueller A. 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. *Anaesthesia*. 2021 Oct;76(10):1342-1351. doi: 10.1111/anae.15469. Epub 2021 May 7. PMID: 33960404.

Sein Beitrag im Einzelnen:

Zusammen mit einem anderen Prüfarzt, Dr. J. Kurth, und mithilfe einer Gruppe von 8 Doktoranden hat er von Juli 2017 bis zum "last-patient-last-visit" Ende Juli 2018 die letzten 26 nicht-kardiochirurgischen Patienten an der Charité Campus Virchow rekrutiert und nachverfolgt. Dies begann mit dem täglichen Screening der Patienten auf In- und Exklusionskriterien und Aufnahme in die Screeningliste. Die Patienten wurden folglich, solange es dazu logistische und personelle Kapazitäten gab, ein oder mehreren Tagen zuvor eingeschlossen. Am Vortag hatte er das pseudonymisierte Prüfmedikament bestellt und die Baseline Daten des Patienten / der Patientin mithilfe eines präoperativen CRFs gesammelt. Am Operationstag war er zuständig für das Ansetzen und Ausschleichen des Prüfmedikaments und begleitete und übernahm, falls keine(n) DoktorandIn dazu vorhanden war, die intra- und postoperative Datensammlung von u.A. der Delirscores, Vitalparametern, verabreichten Medikamenten, BGAs, Schmerz- und Sedierungsscores und jeglichen anhand CRFs. Während der Operation war er zuständig für die Sicherheit des Prüfmedikaments und hätte im Notfall mittels Notfallumschlag entblinden können. Postoperativ plausibilisierte er die von den Doktoranden gesammelten perioperativen Daten der CRFs anhand der OP-Protokolle. Zusätzlich vermerkte er alle möglichen Adverse Events (AEs) und Severe Adverse Events (SAEs) auf einem CRF, die zur Sicherheitsmonitoring des Prüfmedikaments dienten. Dieses überprüfte er im Folgenden zusammen mit der Sicherheitsmonitorin der Studie, Frau Dr. Kathrin Scholtz. Nachdem alle Daten anhand CRFs gesammelt wurden, wurden die Daten von mir und allen Doktoranden in der Datenbank eingetragen. Die Datenbank wurde im Anschluss von ihm und der weiteren Prüfärzten überprüft.

Nach Entschlüsselung und Auswertung der Daten vom Biometrischen Institut durch Frau A. Porth (Institut für Biometrie und Klinische Epidemiologie der Charité Berlin (iBikE)), hatte er als Erstautor die obengenannte Publikation geschrieben (summary, intrudoction, methods, results, discussion conclusion und references außer Figuren und Tabellen, die acknowledgements, die Anteile über neurocognitive Testing, POCD und appendix) und mit den Ko-Autoren diskutiert und finalisiert.

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Unterschrift, Datum und Stempel des/der erstbetreuenden Hochschullehrers/in

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Unterschrift des Doktoranden/der Doktorandin

9. Extract from Journal Summary List for Anesthesiology

Journal Data Filtered By: **Selected JCR Year: 2020** Selected Editions: SCIE,SSCI
Selected Categories: **"ANESTHESIOLOGY"** Selected Category Scheme: WoS
Gesamtanzahl: 33 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	JOURNAL OF CLINICAL ANESTHESIA	5,577	9.452	0.007420
2	BRITISH JOURNAL OF ANAESTHESIA	27,510	9.166	0.029010
3	ANESTHESIOLOGY	33,319	7.892	0.023570
4	PAIN	45,325	6.961	0.031030
5	ANAESTHESIA	13,711	6.955	0.012400
6	REGIONAL ANESTHESIA AND PAIN MEDICINE	7,161	6.288	0.008630
7	ANESTHESIA AND ANALGESIA	31,391	5.108	0.026240
8	Canadian Journal of Anesthesia-Journal canadien d anesthesie	8,032	5.063	0.006390
9	Pain Physician	6,424	4.965	0.006760
10	EUROPEAN JOURNAL OF ANAESTHESIOLOGY	5,302	4.330	0.006910
11	Anaesthesia Critical Care & Pain Medicine	1,101	4.132	0.002510
12	JOURNAL OF NEUROSURGICAL ANESTHESIOLOGY	1,988	3.956	0.001470
13	EUROPEAN JOURNAL OF PAIN	9,204	3.931	0.009110
14	PAIN MEDICINE	10,086	3.750	0.012300
15	Perioperative Medicine	497	3.535	0.001450
16	CLINICAL JOURNAL OF PAIN	8,589	3.442	0.007510
17	Pain Practice	3,187	3.183	0.003750
18	Minerva Anestesiologica	3,446	3.051	0.004060

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
19	Current Opinion in Anesthesiology	3,336	2.706	0.004200
20	JOURNAL OF CARDIOTHORACIC AND VASCULAR ANESTHESIA	7,080	2.628	0.008380
21	INTERNATIONAL JOURNAL OF OBSTETRIC ANESTHESIA	2,060	2.603	0.002360
22	PEDIATRIC ANESTHESIA	5,810	2.556	0.005080
23	JOURNAL OF CLINICAL MONITORING AND COMPUTING	2,519	2.502	0.002810
24	Best Practice & Research-Clinical Anaesthesiology	1,730	2.431	0.001850
25	BMC Anesthesiology	2,964	2.217	0.006400
26	ACTA ANAESTHESIOLOGICA SCANDINAVICA	7,801	2.105	0.005690
27	Journal of Anesthesia	2,733	2.078	0.003100
28	ANAESTHESIA AND INTENSIVE CARE	2,957	1.669	0.002100
29	SCHMERZ	935	1.107	0.000810
30	ANAESTHESIST	1,540	1.041	0.001170
31	ANASTHESIOLOGIE & INTENSIVMEDIZIN	475	1.000	0.000300
32	Revista Brasileira de Anestesiologia	1,288	0.964	0.001360
33	ANASTHESIOLOGIE INTENSIVMEDIZIN NOTFALLMEDIZIN SCHMERZTHERAPIE	439	0.698	0.000220

10. Publication

Anaesthesia 2021 doi:10.1111/anae.15469

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

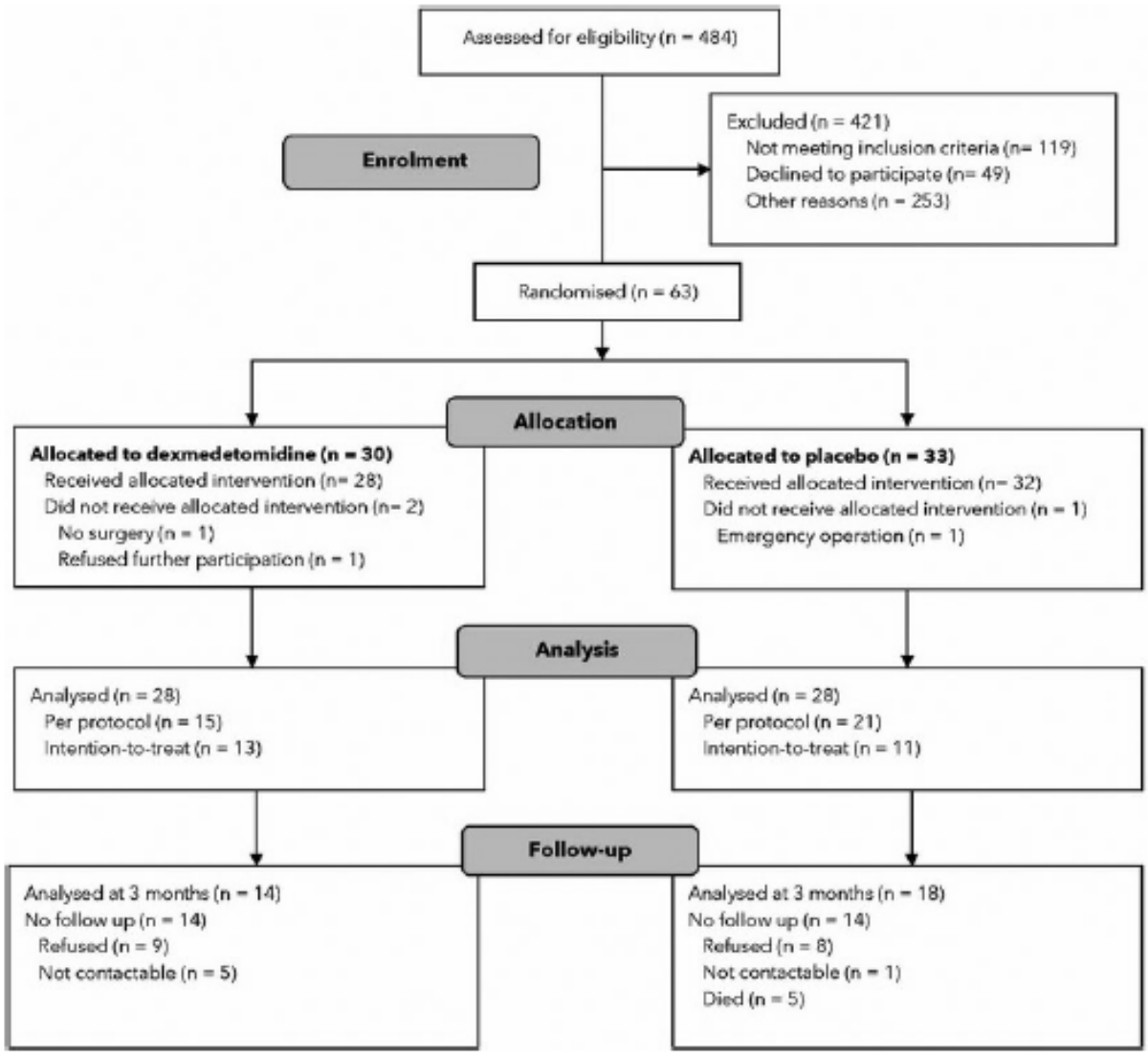

Figure 1 Study flow diagram.

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

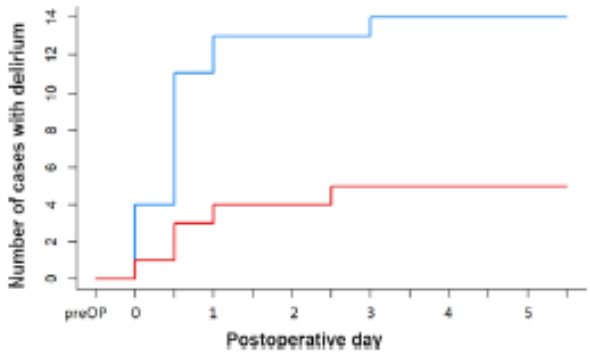

Figure 2 Cumulative case count of delirium in dexmedetomidine (red) and placebo (blue) groups.

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.

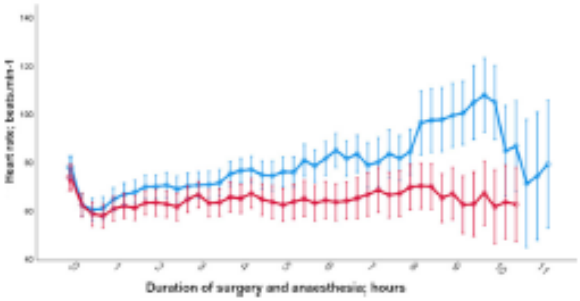

Figure 3 Intra-operative heart rate in dexmedetomidine (red) and placebo (blue) groups. As the duration of surgery increases, the number of patients analysed decreases as demonstrated by the widening of 95%CI bars.

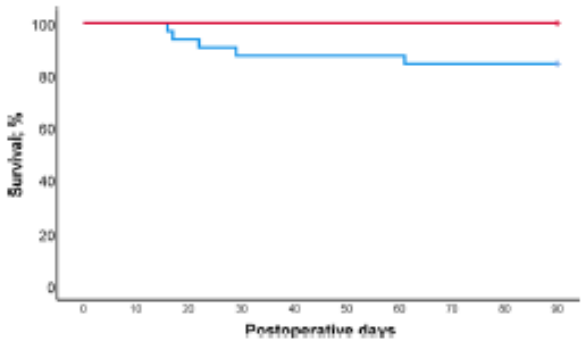

Figure 4 Mortality up to 90 days postoperatively in dexmedetomidine (red) and placebo (blue) groups.

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.

11. Curriculum Vitae

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

12. List of publications

Publication on which this dissertation is centred

van Norden J., Spies C.D., Borchers F., Mertens M., Kurth J.., Heidgen J., Pohrt A. & Mueller A. 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. *Anaesthesia*. 2021 Oct;76(10):1342-1351. doi: 10.1111/anae.15469. Epub 2021 May 7. PMID: 33960404.

Individual contribution: Patient recruitment, study drug administration and safety monitoring, safety evaluation, coordinating a group of research assistants, gathering of data by Case Report Forms, creation and plausibility check of the database, writing of manuscript (abstract, introduction, methods, result, discussion, conclusion)

Publications not related to this dissertation

Bor, A. S., Rinkel, G. J., **van Norden, J**., & Wermer, M. J. Long-term, serial screening for intracranial aneurysms in individuals with a family history of aneurysmal subarachnoid haemorrhage: a cohort study. *The Lancet Neurology*. 2014 Apr;13(4),385–392. doi: 10.1016/S1474-4422(14)70021-3. Epub 2014 Mar 5. PMID: 24618352.

Individual contribution: data collection and proofreading of manuscript

Smarius, B., Breugem, C. C., Boasson, M. P., Alikhil, S., **van Norden, J**., van der Molen, A., & de Graaff, J. C. Effect of hyperextension of the neck (rose position) on cerebral blood oxygenation in patients who underwent cleft palate reconstructive surgery: prospective cohort study using near-infrared spectroscopy. *Clinical Oral Investigations*, 2020 Aug;24(8),2909–2918. doi: 10.1007/s00784-019-03157-8. Epub 2020 Mar 26. PMID: 32219565.

Individual contribution: creation of the study protocol, writing of application for the ethics committee, inclusion of the first 10 patients and proofreading the manuscript

13. Danksagung

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“There are no negatives in life, only challenges to overcome that will make you stronger.”
-Eric Bates-