EJA

Eur J Anaesthesiol 2020; **37:**1–10

ORIGINAL ARTICLE

Effect of dexmedetomidine on Nociception Level Index-guided remifentanil antinociception

A randomised controlled trial

Sean Coeckelenbergh, Stefano Doria, Daniel Patricio, Laurent Perrin, Edgard Engelman, Alexandra Rodriguez, Livia Di Marco, Luc Van Obbergh, Jean-Pierre Estebe, Luc Barvais and Panayota Kapessidou

BACKGROUND The effect of dexmedetomidine on Nociception Level Index-guided (Medasense, Israel) antinociception to reduce intra-operative opioid requirements has not been previously investigated.

OBJECTIVE We aimed to determine if low-dose dexmedetomidine would reduce remifentanil requirements during Nociception Level Index-guided antinociception without increasing complications associated with dexmedetomidine.

DESIGN Double-blind randomised controlled trial.

SETTING Two university teaching hospitals in Brussels, Belgium.

PATIENTS American Society of Anesthesiologists 1 and 2 patients ($n = 58$) undergoing maxillofacial or cervicofacial surgery under propofol–remifentanil target-controlled infusion anaesthesia.

INTERVENTIONS A 30 min infusion of dexmedetomidine, or equal volume of 0.9% NaCl, was infused at 1.2 $\mu g\,kg^{-1}\,h^{-1}$ immediately preceding induction and then decreased to 0.6 $\mu g\,kg^{-1}\,h^{-1}$ until 30 min before ending surgery. Nociception Level Index and frontal electroencephalogram guided the remifentanil and propofol infusions, respectively.

MAIN OUTCOMES The primary outcome was the remifentanil requirement. Other outcomes included the propofol requirement, cardiovascular status and postoperative outcome.

RESULTS Mean ± SD remifentanil (3.96 ± 1.95 vs. $4.42 \pm 2.04\,ng\,ml^{-1}$; $P = 0.0024$) and propofol (2.78 ± 1.36 vs. $3.06 \pm 1.29\,\mu g\,ml^{-1}$; $P = 0.0046$) TCI effect site concentrations were lower in the dexmedetomidine group at 30 min postincision and remained lower throughout surgery. When remifentanil (0.133 ± 0.085 vs. $0.198 \pm 0.086\,\mu g\,kg^{-1}\,min^{-1}$; $P = 0.0074$) and propofol (5.7 ± 2.72 vs. $7.4 \pm 2.80\,mg\,kg^{-1}\,h^{-1}$; $P = 0.0228$) requirements are represented as infusion rates, this effect became statistically significant at 2 h postincision.

CONCLUSION In ASA 1 and 2 patients receiving Nociception Level Index-guided antinociception, dexmedetomidine decreases intra-operative remifentanil requirements. Combined frontal electroencephalogram and Nociception Level Index monitoring can measure dexmedetomidine's hypnotic and opioid-sparing effects during remifentanil-propofol target-controlled infusion anaesthesia.

TRIAL REGISTRATIONS Clinicaltrials.gov: NCT03912740, EudraCT: 2018-004512-22.

Published online xx month 2020

Introduction

Antinociception remains a challenge in peri-operative medicine. Although opioids are fundamental in modern analgesia, they can adversely affect consciousness through sedation, delirium and coma,[1] respiration

From the Department of Anaesthesiology, Erasme University Hospital, Université Libre de Bruxelles, Brussels, Belgium (SC, SD, LP, EE, LVO, LB), Department of Anaesthesiology, Saint Pierre University Hospital, Université Libre de Bruxelles, Brussels, Belgium (SC, DP, LDM, PK), EW Data Analysis, Brussels, Belgium (EE), Department of Ear-Nose-Throat Surgery, Saint Pierre University Hospital, Université Libre de Bruxelles, Brussels, Belgium (AR) and Department of Anaesthesiology, CHU Rennes, Université de Rennes, Rennes, France (JP-E)

Correspondence to Sean Coeckelenbergh, Department of Anaesthesiology, Erasme University Hospital, Université Libre de Bruxelles, Rue Lennik 808, 1070 Brussels, Belgium
Tel: +32 25 55 39 19; e-mail: sean.coeckelenbergh@ulb.be

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DOI:10.1097/EJA.0000000000001402

CE: Tripti; EJA/EJA-D-20-00734; Total nos of Pages: 10;
EJA-D-20-00734

through depression and hypoxaemia,[2,3] digestion through ileus and nausea[4,5] and somatosensation through hyperalgesia.[6–8] Opioid toxicity may be reduced by implementing opioid sparing or even opioid free strategies that take advantage of the synergistic properties of other drugs, such as alpha-2 central agonists or *N*-methyl D-aspartate (NMDA) antagonists.[6,9–11] An additional approach is to only give the required amount of analgesics, but clinical evaluation is often inadequate and anaesthetists too often find themselves one step behind nociception (i.e. the patient's unconscious response to noxious stimuli).[12]

As nociception leads to a sympathetic response, researchers have developed several monitors that can detect small changes in sympathetic tone.[13,14] These measurements can be used as surrogates to clinically evaluate nociception.[15] The PMD-200™ (Medasense, Israel), displays the Nociception Level Index (NOL Index),[16,17] which integrates heart rate, heart rate variability, skin conductance level, number of skin conduction fluctuations and photo-plethysmograph pulse wave amplitude. The NOL Index ranges from 0 (no nociception) to 100 (intense nociception) and the recommended range during surgery is from 10 to 25.

Dexmedetomidine, a potent central alpha-2 agonist, has been shown to have anaesthetic and opioid-sparing effects.[10,18,19] For example, it reduced fentanyl requirements during cholecystectomy[10] and remifentanil requirements during abdominal[18] and nasal surgery.[19] However, previous studies that investigated dexmedetomidine used clinical indicators, such as heart rate and blood pressure or frontal electroencephalogram (EEG) to guide antinociception and consequently have limitations. Heart rate and blood pressure have been shown to be less sensitive and specific to the NOL Index[20] whereas frontal EEG evaluates cortical activity, which is principally affected by anaesthetic depth and its sensitivity to nociception may be severely attenuated in the anaesthetised patient.[21]

The goal of this study was to determine if the antinociceptive effects of a continuous low-dose dexmedetomidine infusion would affect intra-operative remifentanil requirements during NOL Index-guided antinociception without increasing dexmedetomidine-associated complications (e.g., intra-operative bradycardia and hypotension). We also investigated its effects on propofol requirement and postoperative outcomes, pain number rating scale, morphine consumption and opioid-related adverse events.

Materials and methods

Ethics

This study was approved by the Erasme University Hospital and Saint Pierre University Hospital institutional review boards, (Ethics Committee Number P2018/568/B406201837971, Erasme University Hospital, Rue Lennik 808, 1070, Brussels, 18 February 2019) registered on both clinicaltrials.gov (NCT03912740) and EudraCT (2018-004512-22), and approved by the Belgian Federal Agency for Medicines and Health Products. It adheres to the CONSORT guidelines. It was carried out from April 2019 to December 2019. All patients gave written informed consent.

Patients

American Society of Anesthesiologists (ASA) physical status classes 1 and 2 patients undergoing scheduled maxillofacial or cervicofacial surgery that required at least one night in hospital were recruited. Exclusion criteria were ASA score greater than 2, pre-operative organ dysfunction, nonregular cardiac rhythm, implanted pacemakers, emergency surgery, pregnancy, breast-feeding, allergy, intolerance, or contraindications to any of the study drugs, participation in another interventional study, one-day surgery and patient refusal.

Study design

Randomisation, blinding and data collection

Patients were randomised (1 : 1) in blocks of 10 (NCSS, LLC; Kaysville, Utah, USA) by the statistician (EE). The pharmacists in both centres then established the group drug allocation. The Erasme University Hospital pharmacy was responsible for the first five blocks and the Saint Pierre University Hospital pharmacy for the last five. Patients, caregivers and investigators (statistician, anaesthetists, surgeons, nurses) were blinded to the drug allocation, which was known only to the pharmacists. Each hospital pharmacy prepared, stored and dispensed the study drugs, which were placed in a secure refrigerator in the operating theatre at least 1 h before the procedure. Syringes were labelled with the date of preparation, study name and patient number. Investigators remained blinded to the treatment allocation until completion of the statistical analysis. The propofol and remifentanil effect site concentrations (Ce) and total infused dosages were noted during the procedure by the blinded investigator.

Treatment groups

Patients were randomised into two groups and received either dexmedetomidine ($6\,\mu g\,ml^{-1}$) or saline (NaCl 0.9%) at equal infusion volumes. Study drugs were prepared as follows: in the dexmedetomidine group 2 ml of dexmedetomidine $100\,\mu g\,ml^{-1}$ (200 μg) were diluted to 33 ml with saline to give $6.06\,\mu g\,ml^{-1}$ of dexmedetomidine whereas in the saline group, 33 ml of saline was drawn up in a syringe. For practical purposes, we rounded the concentration of dexmedetomidine to $6\,\mu g\,ml^{-1}$.

Once the patient was monitored and the intravenous cannula inserted, a 30-min infusion was started at a rate ($ml\,h^{-1}$) set at the patient's weight divided by 5 ($1.2\,\mu g\,kg^{-1}\,h^{-1}$ for dexmedetomidine and an equal

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volume per weight in the saline group). After this 30 min period, the infusion rate (ml h^{-1}) was decreased to the patient's weight divided by 10 (0.6 μg kg^{-1} h^{-1} for dexmedetomidine and an equal volume per weight in the saline group). The study drug was stopped 30 min before the anticipated end of surgery or if the attending anaesthetist suspected that it was responsible for an adverse event, such as refractory hypotension or bradycardia.

Anaesthesia procedures

Patients fasted for at least 6 h for solids and 2 h for liquids. Premedication consisted of alprazolam 0.5 mg if under 65 years of age, or 0.25 mg if 65 or older. Upon arrival in the operating room, patients were monitored with standard anaesthesia monitoring, frontal EEG (Spectral Entropy, GE Healthcare, Finland, for Saint Pierre University Hospital; and Bispectral Index monitor, Covidien, Ireland, for Erasme University Hospital), and the PMD-200 ^{TM}. The disposable electrode and PMD-200 sensor were placed on the index of the hand contralateral to the blood pressure cuff. The study drug infusion was started immediately after monitoring and intravenous cannulation. Anaesthetists preoxygenated and then induced anaesthesia using effect site target-controlled infusion propofol (TCI) (Schnider Model), which was titrated up until loss of consciousness and frontal EEG was below 60. Remifentanil TCI (Minto model) was progressively increased to a Ce of 4 ng ml^{-1}. An intubation dose of 0.6 mg kg^{-1} of rocuronium was administered upon assuring mask ventilation. Minimum recommended Ce values of remifentanil and propofol were 2 ng ml^{-1} and 1.5 μg ml^{-1}, respectively, but could be further decreased if the attending anaesthetist considered it necessary. Remifentanil was titrated to maintain a NOL Index between 10 and 25 (if NOL was less than 10 for 3 min, remifentanil Ce was decreased by 0.5 ng ml^{-1} every 3 min until NOL reached 10; if NOL was greater than 25, remifentanil Ce was increased by 0.5 ng ml^{-1} every 3 min until NOL reached 25; if NOL was greater than 30 for 30 s, remifentanil Ce was increased by 0.5 ng ml^{-1} every 30 s until NOL reached 30). Smaller changes were allowed if 0.5 ng ml^{-1} steps were linked to over or undershooting of targets. Propofol was titrated to maintain a frontal EEG between 40 and 60. Mean blood pressure was maintained over 65 mmHg in patients under the age of 65 years that did not suffer from hypertension. Patients that were hypertensive pre-operatively (blood pressure over 140/90 mmHg or receiving antihypertensive medication) or who were aged 65 years or older had their mean blood pressure maintained over 75 mmHg. In case of hypotension (mean blood pressure under 65 or 75 mmHg depending on the history), the patient's legs were raised and anaesthetic doses reduced, if excessive. A 100 ml 3-min crystalloid (NaCl 0.9%) mini-fluid challenge was infused and, if insufficient, either ephedrine or phenylephrine was titrated based on heart rate. If hypotension persisted, another 100 ml 3-min fluid challenge was administered. If refractory hypotension occurred, the attending physicians administered additional fluids and vasopressors at their discretion, and if considered necessary, were free to stop the study drug. Anaesthetists administered either nicardipine, labetolol or esmolol if hypertension occurred (intra-operative mean blood pressure ≥100) or if there was a surgical need to decrease blood pressure. In case of bradycardia, atropine was administered at the anaesthetist's discretion and the study drug was stopped if thought necessary. A continuous crystalloid infusion of 3 ml kg^{-1} h^{-1} maintained baseline needs. Paracetamol and diclofenac were administered, unless contraindicated, and all patients concurrently received intravenous morphine 50 μg kg^{-1} 30 min before the end of surgery. Postoperatively, morphine was titrated (2 mg per 5 min) in the postanaesthesia care unit (PACU) if the patient reported a pain number rating scale greater than 3 on a 10 points scale.

Outcomes, data collection and analysis

The primary outcome was the intra-operative requirement of remifentanil (Ce in ng ml^{-1}, and continuous infusion in μg kg^{-1} min^{-1}) to maintain NOL Index between 10 and 25. Required doses of propofol (Ce in μg ml^{-1} and continuous infusion in mg kg^{-1} h^{-1}) to maintain frontal EEG values between 40 and 60 were also investigated. Mean blood pressure, heart rate, frontal EEG, NOL Index, remifentanil Ce and propofol Ce were recorded during key intra-operative periods (before intubation, 1 min post-intubation, 5 min after intubation, before incision, at incision, incision + 5 min, incision + 10 min, incision + 15 min, incision + 30 min and at end of surgery).

Other intra-operative outcomes included estimated blood loss, use of vasoactive or hypotensive drugs, quantity of fluids administered, time to extubation and occurrence of hypotension or hypertension. Postoperative variables included morphine requirements, pain number rating scale, occurrence of postoperative opioid-related side effects (PONV within the first 24 h), postoperative hypoxaemia (need within 24 h postop for additional oxygen to maintain transcutaneous haemoglobin O_2 saturation >94%), postoperative hypopnoea (less than 8 breaths min^{-1}), PACU length of stay (LOS) and hospital LOS.

Furthermore, to distinguish the sympatholytic effect of dexmedetomidine (i.e., the decrease in heart rate), from its potential antinociceptive effect, as both can theoretically affect the NOL Index, a post hoc analysis investigated the difference in NOL Index values during episodes 'high' and 'low' heart rate (i.e., heart rate above or below the average intra-operative heart rate value for all patients).

Sample size

Considering that there were no reliable published data for a pretrial power analysis of the effect of dexmedetomidine on the NOL Index during propofol–remifentanil anaesthesia, an arbitrary number of 50 patients per group

was established. An interim analysis was carried out at roughly half of the planned number of patients. Data analysis was preplanned with an alpha-value of 5% for the interim analysis and final analysis (to maintain a level of significance of 0.05 globally, a calculated P value <0.025 should be obtained for each analysis to be considered statistically significant).

Statistical analysis

Intention-to-treat analysis was carried out on data. Remifentanil ($\mu g\,kg^{-1}\,min^{-1}$) and propofol ($mg\,kg^{-1}\,h^{-1}$) total infused requirements and remifentanil ($ng\,ml^{-1}$) and propofol ($\mu g\,ml^{-1}$) calculated effect site concentrations were compared between the groups by an analysis of covariance using a general linear model, with the duration of surgery for the requirements or the duration of infusion for calculated effect site concentration as covariates. A Tukey–Kramer test was performed to compare the least square means derived from the model for duration of surgery or infusion of 30, 60, 90 and 120 min.

Remifentanil Ce, propofol Ce, NOL Index, frontal EEG, heart rate and mean blood pressure measured at the 10 preplanned moments (induction, 1 min postintubation, 5 min after intubation, preincision, incision, incision + 5 min, incision + 10 min, incision + 15 min, incision + 30 min and at end of surgery) were compared by an analysis of variance for repeated measures with mixed models with treatment arms, time and time × treatment interaction terms. Cumulative amounts of postoperative morphine and the number rating score for pain at 1, 2, 3, 6 and 24 h after arrival in the postoperative care unit were compared by an analysis of variance for repeated measures with mixed models with treatment arms, time and time × treatment interaction terms. Categorical data were compared by χ^2 test or a Fisher exact test and the other continuous nonlongitudinal variables were compared with the Mann–Whitney test.

To determine if a reduction in remifentanil requirements was because of the antinociceptive effects of dexmedetomidine or simply its bradycardic effect, all NOL Index values recorded were divided into four groups to perform an analysis of variance for two fixed factors, the intervention group and the categories of heart rate values classified as 'high heart rate' or 'low heart rate' as compared with the mean value of all intra-operative heart rate values recorded of 68 beats min^{-1}. The difference and 95% confidence interval between the mean values of 'high heart rate' and 'low heart rate' subgroups for each intervention were computed.

Data are given as mean ± SD, median [IQR], or number (%). For all tests, a global two-sided P value less than 0.05 was considered statistically significant, which translates to a P less than 0.025 value for the interim and final analysis. All analyses were performed using the NCSS 19.0.3 statistical package (NCSS, LLC; Kaysville, Utah, USA).

Results

Investigators screened 138 patients from April 2019 to December 2019. A total of 66 patients were recruited, eight of whom were excluded after randomisation. Three patients withdrew from the study and for five investigators were not available (Fig. 1). Baseline characteristics were similar between groups (Table 1).

Fig. 1 CONSORT flow diagram.

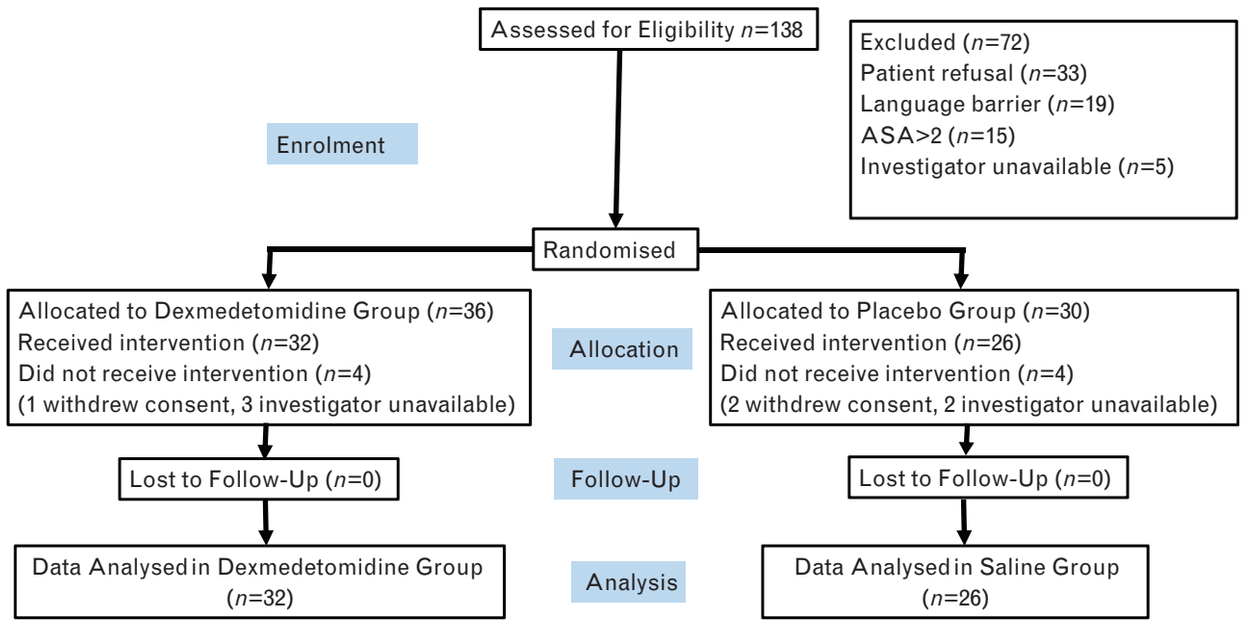


Table 1 Patient data

	Saline ($n=26$)	Dexmedetomidine ($n=32$)	Fisher exact test or χ^2 or Mann–Whitney test P values
Baseline characteristics			
Age (years)	41.7 ± 14.1	45.9 ± 16.3	0.41
Sex M/F	9/17 (34.6%/65.4%)	15/17 (46.9%/53.1%)	0.42
Weight (kg)	77.2 ± 14.5	76.1 ± 16.8	0.61
Height (cm)	172.9 ± 9.2	171.9 ± 8.6	0.81
BMI (kg m^{-2})	25.7 ± 3.9	25.6 ± 4.9	0.70
ASA score (1/2)	10/16 (38.5%/61.5%)	6/26 (18.7%/81.3%)	0.14
SBP pre-op (mmHg)	123 ± 17	127 ± 19	0.48
DBP pre-op (mmHg)	76 ± 12	75 ± 14	0.35
MBP pre-op (mmHg)	92 ± 13	93 ± 14	0.74
HR pre-op (beats min^{-1})	73 ± 10	72 ± 12	0.67
History			
Hypertension	5 (19.2%)	9 (28.1%)	0.54
Diabetes type 1	0	1 (3.1%)	1.00
Diabetes type 2	2 (7.7%)	2 (6.3%)	1.00
COPD	1 (3.9%)	1 (3.1%)	1.00
Asthma	3 (11.5%)	2 (6.3%)	0.64
Alcohol use	12 (46.2%)	15 (46.9%)	1.00
Alcoholism (more than 2 U/day)	3 (11.5%)	6 (19.4%)	0.48
Tobacco	5 (19.2%)	9 (28.1%)	0.54
Chronic antihypertensive therapy			
Beta-blocker	2 (7.7%)	3 (9.4%)	1.00
ACE inhibitor	1 (3.8%)	4 (12.5%)	0.36
Sartan	1 (3.8%)	0 (0%)	0.44
Calcium channel blocker	1 (3.8%)	2 (6.7%)	1.00
Diuretic	0 (0%)	2 (6.2%)	0.49
At least one of beta blocker, ACE inhibitor, sartan, calcium channel blocker, or diuretic	5 (19.2%)	9 (28.1%)	0.54
Surgery type and time			
Cervicofacial/maxillofacial surgery	19/7 (73.1%/26.9%)	22/10 (68.8%/32.2%)	0.27
Duration of anaesthesia (min)	131 ± 54 ~ 129.5 [80.8 to 173]	131 ± 60 ~ 122 [91.5 to 147.8]	0.77
Duration of surgery (min)	97 ± 52 ~ 101 [51 to 134]	97 ± 58 ~ 87 [58 to 115]	0.72

Data given as n (%) or mean ± SD ~ median [interquartile range]. ACE, angiotensin converting enzyme; ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; MBP, mean blood pressure.

Primary outcome

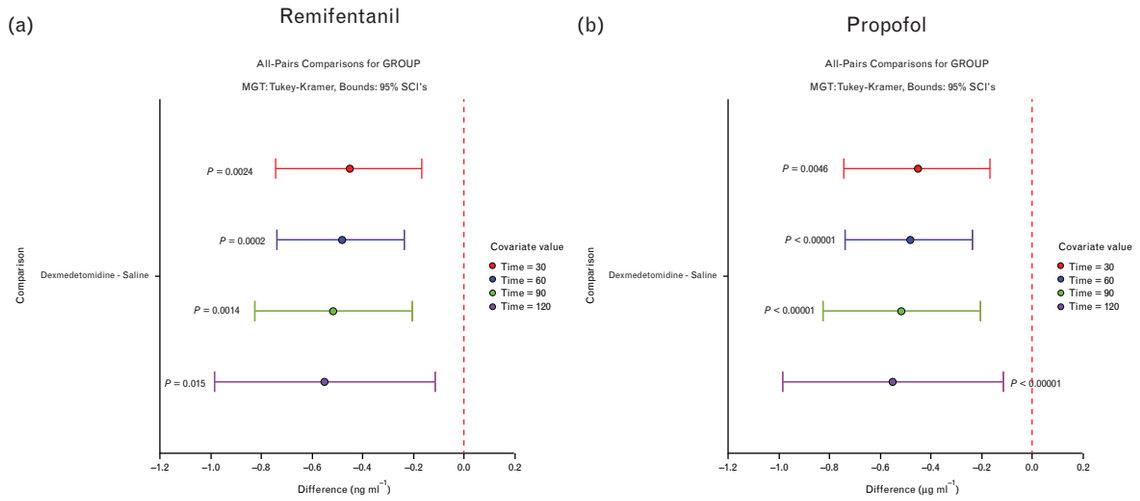
Remifentanil TCI Ce was lower in the dexmedetomidine infusion group (Table 2). Remifentanil TCI Ce (mean ± SD) was lower in the dexmedetomidine group at 30 min post incision (3.96 ± 1.95 vs. 4.42 ± 2.04 ng ml^{-1}; $P=0.0024$) and remained lower at 60 min (4.00 ± 1.75 vs. 4.49 ± 1.67 ng ml^{-1}; $P=0.0002$), 90 min (4.05 ± 2.34 vs. 4.57 ± 2.04 ng ml^{-1}; $P=0.0014$) and 120 min postincision (4.09 ± 3.11 vs. 4.64 ± 2.78 ng ml^{-1}; $P=0.015$) When remifentanil (mean ± SD) requirements are represented as infusion rates, (0.133 ± 0.085 vs. 0.198 ± 0.086 μg kg^{-1} min^{-1}; $P=0.0074$) this effect became statistically

Table 2 Mixed-model comparison of effect site concentrations and intra-operative monitoring signals

	Induction	1 min postintubation	5 min postintubation	Preincision	Incision	5 min postincision	10 min postincision	15 min postincision	30 min postincision	Surgery end	Analysis of variance for repeated measures saline vs. dexmedetomidine
Remifentanil-calculated effect site concentration (ng ml^{-1})											
Saline	4.1 ± 0.8	3.7 ± 1.1	3.0 ± 1.2	3.5 ± 1.5	4.4 ± 1.4	5.2 ± 1.2	5.3 ± 1.4	5.5 ± 1.5	5.4 ± 1.85	4.5 ± 1.95	$P=0.000023$
Dexmedetomidine	4.0 ± 0.8	3.7 ± 1.0	2.9 ± 1.1	3.1 ± 1.2	4.3 ± 0.8	4.6 ± 1.0	4.6 ± 1.2	4.6 ± 1.4	4.5 ± 1.6	3.6 ± 1.6	
Propofol-calculated effect site concentration (μg ml^{-1})											
Saline	3.8 ± 0.8	3.6 ± 0.9	2.9 ± 0.9	2.8 ± 0.9	2.7 ± 0.8	2.8 ± 0.9	2.7 ± 0.8	2.7 ± 0.9	3.0 ± 1.0	2.8 ± 0.9	$P=0.000037$
Dexmedetomidine	4.1 ± 1.5	3.6 ± 1.2	2.7 ± 1.1	2.4 ± 1.0	2.6 ± 1.1	2.4 ± 1.0	2.3 ± 0.9	2.4 ± 1.2	2.5 ± 1.3	2.1 ± 1.1	
Nociception level index											
Saline	18 ± 13	34 ± 20	20 ± 18	23 ± 19	29 ± 17	23 ± 15	22 ± 16	15 ± 13	10 ± 7	8 ± 7	$P=0.47$
Dexmedetomidine	20 ± 15	39 ± 19	17 ± 17	14 ± 13	25 ± 15	17 ± 16	18 ± 14	17 ± 12	15 ± 11	10 ± 11	
Frontal EEG index											
Saline	48 ± 16	45 ± 9	45 ± 10	47 ± 10	42 ± 10	40 ± 8	44 ± 8	47 ± 8	47 ± 7	48 ± 9	$P=0.0017$
Dexmedetomidine	50 ± 17	40 ± 13	39 ± 12	42 ± 9	40 ± 7	40 ± 9	43 ± 7	45 ± 8	42 ± 7	44 ± 8	
Heart rate (beats min^{-1})											
Saline	67 ± 12	73 ± 12	72 ± 13	72 ± 13	71 ± 14	71 ± 14	72 ± 14	69 ± 14	68 ± 15	68 ± 17	$P=0.00017$
Dexmedetomidine	62 ± 15	67 ± 15	70 ± 19	66 ± 10	66 ± 10	63 ± 16	66 ± 12	68 ± 11	65 ± 10	65 ± 12	
Mean blood pressure (mmHg)											
Saline	87 ± 16	89 ± 16	84 ± 10	84 ± 11	86 ± 14	87 ± 15	91 ± 18	91 ± 17	89 ± 14	81 ± 3	$P=0.00012$
Dexmedetomidine	83 ± 14	85 ± 21	81 ± 17	83 ± 13	81 ± 12	80 ± 9	78 ± 8	83 ± 13	86 ± 11	82 ± 9	

Data represented as mean ± SD.

Fig. 2 Outcome: effect site concentration of remifentanil (panel a) and propofol (panel b) during anaesthesia



The least squares mean differences between the saline group and the dexmedetomine group for duration of infusion of 30, 60, 90 and 120 min are displayed along with the simultaneous 95% confidence interval for the difference (the error bars). A reference line is displayed at difference = 0. *P* values for Tukey–Kramer tests are given for each comparison.

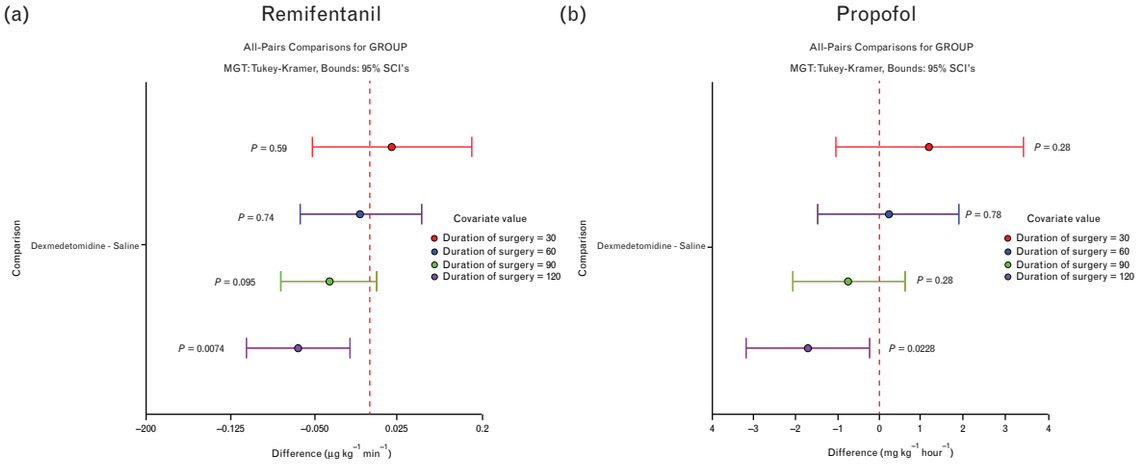
significant at 2 h post incision. (Figs. 2 and 3, Supplementary Table 1 and 2, http://links.lww.com/EJA/A440, http://links.lww.com/EJA/A441).

Secondary outcomes

Propofol TCI Ce, heart rate, blood pressure and frontal EEG all decreased with dexmedetomidine infusion, whereas the NOL Index was similar in both groups (Table 2). The study drug was stopped in two patients (Table 3). Propofol TCI Ce paralleled remifentanil requirements with values (mean ± SD) being consistently lower in the dexmedetomidine group at 30 min (2.78 ± 1.36 vs. $3.06 \pm 1.29\ \mu g\ ml^{-1}$; $P = 0.0046$) 60 min (2.58 ± 1.17 vs. $2.99 \pm 1.11\ \mu g\ ml^{-1}$; $P < 0.00001$), 90 min (2.39 ± 1.56 vs. $2.91 \pm 1.29\ \mu g\ ml^{-1}$; $P < 0.00001$) and 120 min post incision (2.19 ± 2.14 vs. $2.83 \pm 1.85\ \mu g\ ml^{-1}$; $P < 0.00001$) (Fig. 2, Supplementary Table 1, http://links.lww.com/EJA/A440).

When propofol requirements are represented as infusion rates (mean ± SD), this effect became statistically significant

Fig. 3 Outcome: total amounts of remifentanil (panel a) and propofol (panel b) infusions during anaesthesia



The least squares mean differences between the saline group and the dexmedetomidine group for duration of surgery of 30, 60, 90 and 120 min are displayed along with the simultaneous 95% confidence interval for the difference (the error bars). A reference line is displayed at difference = 0. *P* values for Tukey–Kramer tests are given for each comparison.

Table 3 Peri-operative data

	Saline $n = 26$	Dexmedetomidine $n = 32$	Fisher exact test or χ^2 Mann-Whitney test *P*-values
	Intra-operative data		
Study drug stopped	1 (3.8%)	1 (3.1%)	0.92
Time from anaesthesia end to extubation (min)	9.6 ± 14.6 ~ 5.0 [4.0 to 10.25]	8.7 ± 5.7 ~ 8 [5.25 to 11.75]	0.23
Any haemodynamic instability	16 (61.4%)	23 (71.9%)	0.57
Tachycardia			
Heart rate above 90 beats min^{-1}	6 (23.1%)	6 (18.8%)	0.75
Heart rate above 100 beats min^{-1}	2 (7.7%)	0 (0%)	0.2
Heart rate above 120 beats min^{-1}	0 (0%)	0 (0%)	1.00
Bradycardia			
Heart rate under 45 beats min^{-1}	2 (7.7%)	3 (9.4%)	1.00
Heart rate under 40 beats min^{-1}	1 (3.9%)	1 (3.1%)	1.00
Heart rate under 35 beats min^{-1}	0 (0%)	0 (0%)	1.00
Bradycardia requiring atropine	1 (3.9%)	1 (3.1%)	1.00
Hypotension			
Hypotension	4 (15.4%)	14 (43.8%)	0.043
Hypotension requiring vasopressor	4 (15.4%)	12 (37.5%)	0.08
Hypertension			
Hypertension	13 (50%)	12 (37.5%)	0.43
Hypertension requiring treatment	9 (34.6%)	5 (15.6%)	0.085
Intra-operative fluids			
Fluids (ml)	793 ± 509 ~ 725 [500 to 953]	658 ± 235 ~ 600 [463 to 800]	0.31
Blood loss (ml)	41.6 ± 61.1 ~ 1.0 [0.0 to 50.0]	57.6 ± 74.3 ~ 50 [0.0 to 94)	0.30
Fluid balance (ml)	752 ± 516 ~ 675 [400 to– 868]	579 ± 254 ~ 525 [406 to 765]	0.14
	Postoperative data		
Adverse events			
PONV	5 (19.2%)	6 (18.8%)	1.00
Postoperative oxygen required	14 (53.9%)	22 (66.8%)	0.29
Oxygen saturation <94%	9 (34.6%)	10 (31.3%)	1.00
Hypoventilation	5 (19.2%)	9 (28.1%)	0.54
Hypotension	0 (0%)	3 (9.4%)	0.25
Hypertension (MBP above 100 mmHg)	15 (57.7%)	11 (34.4%)	0.11
Hypertension (MBP above 120 mmHg)	2 (7.7%)	1 (3.1%)	0.58
Length of stay			
PACU LOS (days)	5.8 ± 6.8 ~ 3.0 [2.0 to 4.4]	6.2 ± 6.8 ~ 3.0 [2.25 to 5.0]	0.45
Hospital LOS (days)	1.89 ± 1.03 ~ 2 [1 to 2]	2.00 ± 0.76 ~ 2 [1.25 to 2]	0.29

Data given as *n* (%) or mean ± SD ~ median [interquartile range]. MBP, mean blood pressure; LOS, length of stay; PACU, postanaesthesia care unit; PONV, postoperative nausea or vomiting.

at 2 h post incision (5.7 ± 2.72 vs. 7.4 ± 2.80 mg kg^{-1} h^{-1}; $P = 0.0228$) (Fig. 3, Supplementary Table 2, http://links.lww.com/EJA/A441). There was a tendency towards more episodes of hypotension in the dexmedetomidine group requiring Trendelenburg position and a mini-fluid challenge (15.4 vs. 43.8%, $P = 0.043$) and vasopressor administration (15.4 vs. 37.5% $P = 0.08$). There was also a trend towards more hypertension requiring treatment in the saline group (34.6 vs. 15.6%, $P = 0.085$) (Table 3).

Post hoc analysis results indicated that for heart rate values under 68 beats min^{-1}, the NOL Index values decreased in both the saline (22.8 ± 15.3 vs. 14.3 ± 15.4; $P < 0.001$) and dexmedetomidine (21.3 ± 15.3 vs. 16.2 ± 15.4; $P = 0.001$) groups. Furthermore, differences in NOL Index values between saline and dexmedetomidine when divided into subgroups of 'low heart rate' and 'high heart rate' were not different (Supplementary Table 3, http://links.lww.com/EJA/A442).

Morphine requirements, postoperative pain number rating scale and opioid-related complications (postoperative nausea or vomiting, hypoxaemia or bradypnoea) were not statistically different between groups (Table 3, Supplementary Table 4, http://links.lww.com/EJA/A443, Supplementary Figure 1, http://links.lww.com/EJA/A439). No other peri-operative adverse events were reported. There was no significant difference between groups in postoperative length of stay both in the PACU and in hospital (Table 3).

The trial was stopped as a statistically significant difference between groups for the primary outcome was found after the interim analysis.

Discussion

During NOL Index-guided intra-operative antinociception, patients receiving dexmedetomidine required less remifentanil. The amount of propofol titrated under guidance by frontal EEG was also less in the dexmedetomidine group (Figs. 2 and 3). These differences with the control group may be because of a combination of causes including dexmedetomidine's synergistic antinociceptive and hypnotic effects during steady state anaesthesia as well as its sympatholytic activity. Both heart rate

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and blood pressure decreased in the dexmedetomidine group, probably because of the haemodynamic effects of the central alpha-2 agonist.[22]

Peri-operative monitoring is essential for good patient care. In contemporary medicine, almost every component of anaesthesia can be monitored (e.g., hypnotic depth,[23] neuromuscular blockade,[24] haemodynamic optimisation[25]) but antinociception monitoring has only recently been introduced into operating rooms.[26] Despite their capacity to guide therapy, monitors can be affected by many cofactors. The dose-dependent effect of ketamine on frontal EEG signal is a well established example.[27] Available nociceptive monitors are principally concerned with opioids and little has been published on the effects of opioid-sparing agents in conjunction with them. In this study, we show that a low dose of dexmedetomidine does affect the NOL Index signal and leads to reduction in intra-operative opioids when applying a goal-directed antinociceptive strategy.

Le Guen *et al.* have previously demonstrated that during closed-loop propofol and remifentanil anaesthesia guided with the Bispectral Index, dexmedetomidine administration reduced remifentanil and propofol requirements for intubation. Intra-operatively, however, only propofol requirements decreased.[18] Their research diverged on several points from the current study. Most importantly, remifentanil administration was guided by changes in frontal EEG and not with the NOL Index. These monitors evaluate different pathways in nociception as frontal EEG focuses on cortical activity, whereas the NOL Index monitors sympathetic response. These two types of monitors probably differ in sensitivity, specificity and therapeutic thresholds.[13] In addition, Le Guen *et al.* used a closed-loop system for remifentanil and propofol administration. Such a system performs better than anaesthetists at maintaining targets, and thus may be the reason why they had better haemodynamic stability.[28] Unfortunately, closed-loop systems are not yet available on a large scale and most clinicians do not use these tools. In our study, propofol Ce was manually adapted to maintain frontal EEG indexes within the recommended ranges to prevent adverse events, such as hypotension, burst suppression, awareness and postoperative cognitive dysfunction.[29]

An important observation is that as surgery progressed, remifentanil Ce barely changed and infusion rates only slightly decreased in the dexmedetomidine group, whereas both remifentanil TCI Ce and infusion rates increased in the saline group (Supplementary Tables 1, http://links.lww.com/EJA/A440 and 2, http://links.lww.com/EJA/A441). This could partially be explained by the phenomenon of opioid-induced tolerance,[30] which may be inhibited by dexmedetomidine. However, propofol TCI Ce decreased in both groups as intra-operative time progressed, whereas propofol infusion requirements actually increased in the saline group (Supplementary Tables 1, http://links.lww.com/EJA/A440 and 2, http://links.lww.com/EJA/A441). This may be due, in part, to the bradycardic effects of dexmedetomidine. Previous research has shown that opioids, via their bradycardic effects, can reduce cardiac output and hepatic blood flow. This can lead to a decrease in propofol metabolism and an increase in plasma propofol levels (decreased requirements).[31] Central alpha-2 agonists also decrease heart rate and could consequently slow propofol's metabolism, but plasma drug levels of propofol were not investigated as this was not the purpose of our study. However, we did measure processed frontal EEG values, which were in target, but still significantly lower, in the dexmedetomidine group (Table 2). This gives us an a priori indication of dexmedetomidine's possible direct (by perhaps decreasing the requirements of propofol to act on gamma-aminobutyric acid receptors) or indirect (by possibly reducing hepatic blood flow and increasing propofol plasma levels) synergistic effects on the hypnotic component of anaesthesia. As the focus of our study was antinociception, we did not carry out an analysis of the EEG spectrogram. A future analysis of the frequency distributions could clarify the effects of combining these hypnotics on cortical neurophysiology.[32] Future electroencephalographic, pharmacodynamic and pharmacokinetic studies may determine dexmedetomidine's effects on the metabolism of remifentanil and propofol.

Despite our goal-directed strategy, patients in the low-risk cohort that received dexmedetomidine had lower blood pressure, heart rate and frontal EEG values. The incidence of bradycardia requiring atropine, however, was not significantly different between groups (3.9 vs 3.1%, $P = 1.00$). On the other hand, the incidence of hypotension was markedly increased in the dexmedetomidine group (43.8% vs. 15.4%, $p=0.043$), but did not reach the statistically significant threshold for the interim analysis (i.e., $P<0.025$). As intra-operative hypotension was not the primary outcome, these results remain exploratory. Future studies should focus on the incidence of hypotension as a primary outcome to determine if dexmedetomidine as an adjunct to goal-directed remifentanil–propofol anaesthesia leads to more hypotension. Postoperative morphine requirements, pain number rating scale and adverse events were not significantly different between groups. This was perhaps because of the relatively low level of pain associated with the selected surgical procedures, the anticipated dose of morphine administered before the end of surgery, the low dose of dexmedetomidine infused or simply that the current study is underpowered for these outcomes. Exploratory data is consequently inconclusive on the impact of dexmedetomidine on postoperative opioid-related adverse events in this population.

This bicentre double-blind randomised controlled trial had both strengths and limitations. The primary outcome, remifentanil consumption, was guided by the

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NOL Index. This monitor offers a more objective approach to antinociception than the often subjective nature of clinical management, and we have shown that its signal decreases in parallel with dexmedetomidine's pharmacodynamic effects. In addition, the intention-to-treat analysis allows this study to be applied to clinical practice. However, there were also several limitations. As no data were available on the effect of dexmedetomidine on NOL Index-guided remifentanil antinociception, no power analysis was done. Nonetheless, an interim analysis was carried out with a corrected *P* value to reduce alpha error. Also, heart rate reduction may play a role in reducing NOL Index values. The sympatholytic effect of dexmedetomidine could have been at least in part responsible for the reduced use of remifentanil and consequently is a possible confounding factor. Other drugs, such as chronically prescribed beta-blockers, may also influence the NOL. Only five patients received chronic beta-blockade in this study and a post hoc analysis of this subgroup would not be powerful enough to give conclusive results. The use of a closed-loop system would have probably increased the compliance to frontal EEG targets for propofol infusion and could have possibly reduced the incidence of hypotension. As it is only available in one of our two centres, its use was prohibited in the current study. Our design, which omitted the use of a closed-loop, thus offers a practical perspective of contemporary anaesthesia. Another limitation was that delirium, a possible complication of anaesthesia, was not considered as an outcome. However, both centres systematically assessed patients for signs of delirium during their standard PACU evaluation and no cases were reported in the medical records. As this was not a study outcome it is possible that, given the sometimes subtle presentation of hypoactive delirium, certain patients were not diagnosed.[33]

Future directions

In the present study, we show the effect of dexmedetomidine on remifentanil requirements during a goal-directed antinociceptive strategy. Future research should focus on the effects of potential confounders, such as beta-blockers. In addition, researchers should continue to investigate the effect of nonopioid analgesics on nociception monitoring signals and their impact on patient outcome. Furthermore, as opioid-sparing agents, such as clonidine and ketamine, often participate in the hypnotic component of anaesthesia, more thorough studies could determine their combined electroencephalographic signatures during multimodal anaesthesia.

Conclusion

In ASA 1 and 2 patients receiving NOL Index-guided antinociception, dexmedetomidine reduces intra-operative remifentanil requirements. Combined frontal EEG and NOL Index monitoring can measure dexmedetomidine's hypnotic and opioid-sparing effects during remifentanil–propofol anaesthesia.

Acknowledgements relating to this article

Assistance with the study: we would like to thank the Vesalius Association for their research grant. We would also like to thank Tamara Zec, Francesco Zuccarini, Iulia Scolobiuc and Hugues Baelongandi, for their help in collecting data and Serge Carlier for co-ordinating drug preparation and blinding between the two study centres.

Financial support and sponsorship: funding for this study was provided by the Vesalius Association Research Grant (Research award 2019) and departmental resources (Department of Anaesthesiology, Erasme University Hospital, Brussels, Belgium and Department of Anaesthesiology, Saint-Pierre University Hospital, Brussels, Belgium)

Conflicts of interest: SC has received an honorarium from Medasense for a scientific presentation

Presentation: data were presented at the NOL Webinar – Into the Future of Pain Management.

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