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DEXMEDETOMIDINE REDUCES INTRAOCULAR PRESSURE, INTUBATION RESPONSES AND ANAESTHETIC REQUIREMENTS IN PATIENTS UNDERGOING OPHTHALMIC SURGERY

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SUMMARY

We studied the effects of a single i.v. dose of dexmedetomidine, a highly selective and specific alpha$_2$ adrenoceptor agonist, on intraocular pressure (IOP), haemodynamic and sympathoadrenal responses to laryngoscopy and tracheal intubation, and on anaesthetic requirements in ophthalmic surgery. Thirty ASA I–II patients undergoing cataract surgery were allocated randomly to receive either dexmedetomidine 0.6 μg kg^{-1} or saline placebo i.v. 10 min before induction of anaesthesia in a double-blind design. After dexmedetomidine there was a 34% (95% confidence interval (CI) 27–43%) reduction in IOP (P < 0.001) and 62% (CI 57–68%) decrease in plasma noradrenaline concentrations (P < 0.001). After intubation, maximum heart rate was 18% (CI 3–33%, P = 0.036) and the maximum IOP 27% (CI 11–43%, P = 0.005) less in the dexmedetomidine group compared with the patients treated with placebo. Within 10 min after intubation, maximum systolic and diastolic arterial pressures were also significantly (P = 0.013 and P = 0.020) smaller in the dexmedetomidine group. The induction dose of thiopentone was smaller (23% (CI 20–26%) P = 0.012), and the use of isoflurane or fentanyl supplements during anaesthesia was less frequent in the dexmedetomidine group. The patients premedicated with dexmedetomidine recovered faster from anaesthesia (P = 0.042). These results suggest that dexmedetomidine may be a useful anaesthetic adjunct in ophthalmic surgery.

KEY WORDS

Eye: intraocular pressure. Intubation, tracheal: sympathoadrenal response. Sympathetic nervous system: α adrenergic agonist, dexmedetomidine.

The goal of anaesthetic management during ophthalmic surgery is to provide good control of intraocular pressure (IOP), an immobile, uncongested operative field and cardiovascular stability, combined with an adequate level of anaesthesia [1, 2]. In geriatric patients, who frequently have several co-existing diseases, these objectives may often be achieved safely using regional anaesthesia, but in younger patients and in major ophthalmic surgery, general anaesthesia is often considered the method of choice [3–5]. Various pharmacological interventions and anaesthetic techniques have been used to modify the IOP increases and cardiovascular responses after laryngoscopy and tracheal intubation, but none has been entirely successful [1, 2, 4–6].

Clonidine, a centrally acting alpha$_2$ adrenoceptor agonist and antihypertensive agent, reduces anaesthetic requirements, improves perioperative haemodynamic and adrenergic stability and reduces IOP [7–9]. Dexmedetomidine is the pharmacologically active D-isomer of medetomidine, a highly selective, specific and potent alpha$_2$ adrenoceptor agonist [10]. Medetomidine has a considerably higher alpha$_2$:alpha$_1$ selectivity ratio than clonidine in receptor binding experiments and, compared with clonidine, dexmedetomidine may have more efficacy at alpha$_2$ adrenoceptors [10, 11].

Dexmedetomidine has potent hypnotic–anaesthetic actions in rats, mediated via central alpha$_2$ adrenoceptors [12]. In recent studies, i.v. dexmedetomidine was shown to reduce the requirements for thiopentone and isoflurane during gynaecological surgery [13, 14]. In addition, it decreased both normal and increased IOP in studies with awake rabbits [15]. Therefore, we designed a double-blind, placebo-controlled study to evaluate the effects of dexmedetomidine on IOP and sympathoadrenal and cardiovascular responses to laryngoscopy and tracheal intubation, and its influence on anaesthetic requirements during ophthalmic surgery.

PATIENTS AND METHODS

We studied 30 ASA I–II patients of both sexes, aged 65 yr or less (range 18–65 yr), undergoing surgical cataract extraction (table I). All gave written informed consent. Patients with cardiovascular medications likely to affect the response to the trial medication were excluded. The study was approved

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by the Ethics Committee of Turku University Hospital and the Finnish National Board of Health was informed.

Design of the study

The trial was a placebo-controlled phase II study. The patients were allocated randomly (balanced randomization using a computer program, block size 10) to receive either dexmedetomidine 0.6 μg kg^{-1} (0.06 ml kg^{-1}) ($n = 15$) or an equal volume of saline ($n = 15$) i.v. in 1 min 10 min before induction of anaesthesia. The dose of dexmedetomidine was based on the results of the previous phase II studies [13]. The study was conducted in a double-blind fashion. The coded ampoules were supplied by Orion Corporation Farmos, R&D Pharmaceuticals, Turku, Finland.

The patients entered the hospital 1 or 2 days before the scheduled surgery. Routine clinical chemistry tests, ECG and chest x-ray were performed. All patients received oral diazepam 5 mg 90 min before surgery, which was performed between 08:00 and 12:00. After the arrival of the patient in the operating unit, ECG and heart rate (Olli Monitor 431 D, Kone Corporation, Espoo, Finland) were monitored continuously and non-invasive recording of systolic and diastolic arterial pressures at 5-min intervals were started with an automated oscillometric device (Sphygmomanometer 103 N, Nippon Colin, Tokyo, Japan). A vein in the right antecubital fossa was cannulated for blood sampling, and a second cannula was inserted into the dorsum of the left hand for i.v. infusion (2.5% glucose in 0.45% saline, 6–8 ml kg^{-1} h^{-1}) and administration of drugs.

Anaesthetic management

Before induction of anaesthesia, glycopyrronium 4 μg kg^{-1} and fentanyl 2 μg kg^{-1} were administered i.v.

Patients were preoxygenated with 100% oxygen via a facemask (oxygen flow 9 litre min^{-1}). The induction dose of thiopentone was defined as described by Dundee and colleagues [16]: thiopentone 1.5–2 mg kg^{-1} (to the nearest 25 mg) was injected within 10 s and further increments of 25–50 mg at 15-s intervals were given i.v. until disappearance of the eyelash reflex. The patient's lungs were then ventilated manually with 100% oxygen. Pancuronium 0.1 mg kg^{-1} was administered to produce neuromuscular block, which was monitored with a peripheral neurostimulator (Innervator NS 252, Fisher & Paykel Electronics Ltd, Auckland, New Zealand). After disappearance of the twitch response, the duration of laryngoscopy was standardized at 10 s from the moment the vocal cords were seen before tracheal intubation. After intubation, mechanical ventilation of the lungs (Servo 900 B, Siemens Elema, Solna, Sweden) was started and anaesthesia was maintained with 70% nitrous oxide in oxygen. Fentanyl 1 μg kg^{-1} and isoflurane were administered according to the predetermined criteria (see below). Ventilation was adjusted to maintain the end-tidal P_{CO_2} at 4.5–5.5 kPa (Cardiocap, Datex Instrumentarium Corporation, Helsinki, Finland). For further neuromuscular block, additional doses of pancuronium 1–2 mg were given according to the train-of-four response.

Anaesthetic management was designed to maintain arterial pressure and heart rate within 20% limits of the preoperative values and within clinically acceptable limits (systolic arterial pressure greater than 80 mm Hg and less than 180 mm Hg). Preoperative values were defined as the mean of the recordings made on the previous day and immediately before the trial medication.

Hypertension and tachycardia were treated primarily by deepening anaesthesia with 1-μg kg^{-1} doses of fentanyl i.v. or with isoflurane in 0.5% increments in the inhaled concentration. Hypotension (reduction in arterial pressure of 20% or more from the baseline) was treated primarily by increasing the i.v. infusion rate, by reducing isoflurane concentration, and with 3-mg bolus doses of etilefrine, a direct $alpha_1$ sympathomimetic agent. For bradycardia, defined as heart rate less than 45 beat min^{-1}, i.v. glycopyrronium 0.2 mg was readily available. Isoflurane administration was terminated about 10 min before the end of surgery and nitrous oxide administration was terminated at the moment when neuromuscular block was antagonized with glycopyrronium 10 μg kg^{-1} and neostigmine 50 μg kg^{-1}.

After operation, patients were monitored in the recovery room until there were no signs of drug-induced adverse effects (e.g. excessive tiredness, hypotension, postoperative restlessness), but at least for 3 h. For postoperative pain control, oxycodone was administered in incremental doses of 3 mg i.v.

Clinical assessments

Arterial pressure and heart rate were recorded 15 and 1 min before administration of the test drug, 5 and 1 min before induction, at 2-min intervals until 10 min after induction, at 5-min intervals during the rest of the surgery and at 15-min intervals in the recovery room. ECG monitoring was continued throughout the study.

After topical application of local anaesthetic (0.4% oxybuprocaine hydrochloride) IOP was measured with a Schiötz tonometer 2 min before premedication, 2 min before induction, 1 min after induction and 1, 2 and 5 min after intubation. All measurements were performed on the eye which was not to be operated. The average value of three readings was recorded at each time.

The induction dose of thiopentone, the concentration and the administration time of isoflurane, the total amount of fentanyl needed during operation and the eventual need for etilefrine or other medications were recorded. The number of interventions needed during anaesthesia, the time between the termination of nitrous oxide inhalation and the recovery of consciousness (response to a verbal command) was recorded, as was the amount of oxycodone needed in the recovery room.

Biochemical measurements

Blood samples were collected 1 min before administration of the test drug, 1 min before induction, 1 min after induction and 1 min after intubation for the measurement of plasma concentrations of norad-

renaline, 3,4-dihydroxyphenylglycol (DHPG) and adrenaline in plasma. The blood was collected into chilled polypropylene tubes with K_2EDTA, which were stored in ice until centrifuged within 2 h at 0–4 °C. The plasma samples were stored at −70 °C until required for assay. The concentrations of noradrenaline, DHPG and adrenaline in the plasma were measured using high pressure liquid chromatography with coulometric electrochemical detection [17, 18].

The reproducibility of the assay was tested using pooled plasma samples from previous clinical studies, and the resulting intra-assay coefficients of variation (CV) were less than 2 % for noradrenaline, about 4 % for DHPG and approximately 10 % for adrenaline in the relevant concentration ranges. All the samples from one experimental session were analysed in the same batch.

Statistical analysis

Patient characteristics and baseline data were compared with Student's *t* test or Fisher's exact test. Analysis of variance (ANOVA) for repeated measurements with one between-factor (drug) and one within-factor (time) was used for IOP and plasma catecholamine data. Greenhouse–Geisser adjusted *P* values are reported in cases of violation of the sphericity assumption. In a case of a significant drug × time interaction in ANOVA, the analysis was continued by calculating contrasts for the clinically most relevant comparisons. The maxima and minima of the cardiovascular variables and IOP were compared with Student's *t* test. The number of patients needing etilefrine, additional fentanyl and isoflurane was compared with Fisher's exact test; all other data concerning anaesthetic requirements were tested with Student's *t* test, or in case of non-normal distributions, with the Mann–Whitney *U* test.

Results are expressed as mean (SEM) or as median (range); 95 % confidence intervals (CI) were calculated for the main end points. $P < 0.05$ was considered statistically significant.

All statistical work was undertaken at Orion Corporation Farmos, R&D Pharmaceuticals, using BMDP and SAS softwares in a VAX 3100 computer with the VMS operating system.

RESULTS

The patient groups were comparable in gender distribution, age, body weight and resting values of arterial pressure, heart rate and IOP (table I). Dexmedetomidine was well tolerated and no serious drug-related side-effects were recorded. Hypotension (decrease of more than 20 % of baseline) during surgery was treated with etilefrine in four subjects, three in the dexmedetomidine group ($P = 0.60$, Fisher's exact test). None of the patients needed additional treatment for bradycardia, defined as a heart rate less than 45 beat min^{-1}. No ECG abnormalities were observed. The median (range) duration of surgery was 49 min (21–80 min) in the dexmedetomidine group compared with 66 min (26–128 min) in the placebo group ($P = 0.062$, Mann–Whitney *U* test).

Heart rate and arterial pressure

The increase in heart rate associated with laryngoscopy and tracheal intubation was attenuated

TABLE I. *Patient characteristics (mean (SEM) [range]). Dex. = Dexmedetomidine. No statistically significant differences between groups*

	Placebo	Dex.
Age (yr)	48 [18–65]	47 [28–62]
Weight (kg)	77 (4) [53–115]	78 (4) [51–100]
Height (cm)	171 (3) [150–191]	172 (3) [156–186]
Sex (M:F)	8:7	9:6
Preoperative		
IOP (mm Hg)	13 (1) [8–17]	14 (1) [8–19]
HR (beat min^{-1})	71 (2) [58–81]	71 (2) [58–84]
SAP (mm Hg)	131 (5) [95–165]	132 (4) [100–165]
DAP (mm Hg)	79 (3) [60–90]	81 (3) [60–100]

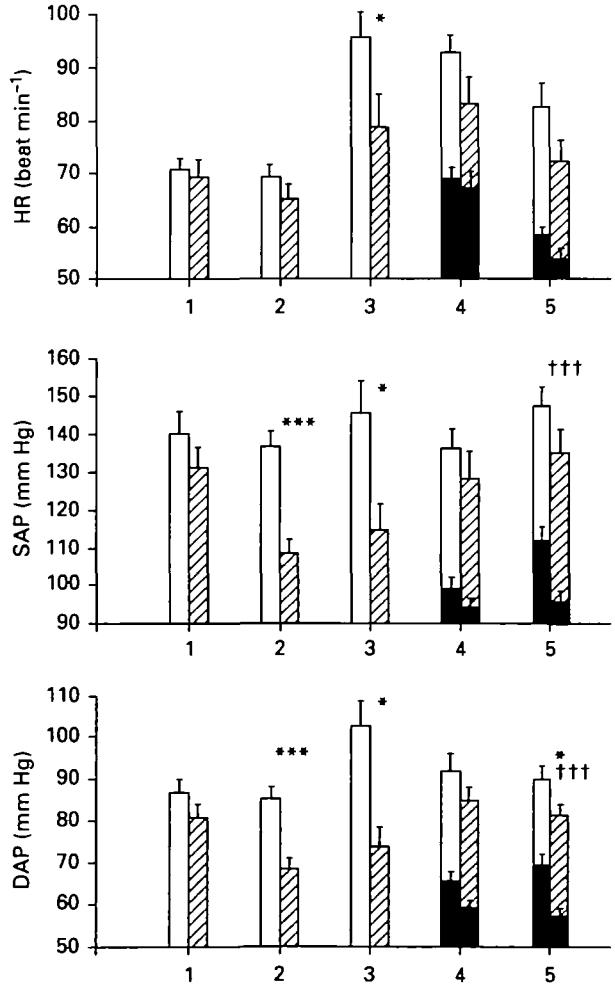

FIG. 1. Heart rate (HR), systolic (SAP) and diastolic (DAP) arterial pressure (mean (SEM) at baseline (1), at induction (2) and means (SEM) of individual maxima and minima (black columns) over time after intubation (3), during operation (4) and in the recovery ward (5)). □ = Placebo group; ▨ = dexmedetomidine group. *$P < 0.05$; ***$P < 0.001$ between groups. †††$P < 0.001$ compared with minima.

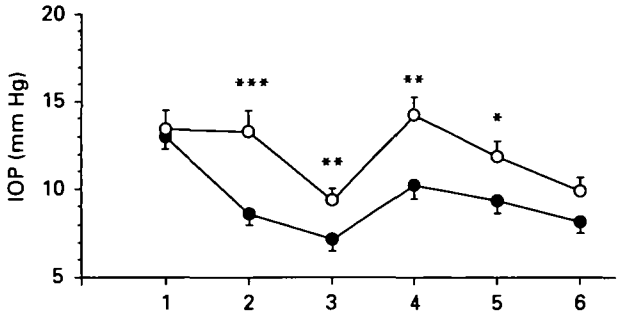

FIG. 2. Mean (SEM) intraocular pressure (IOP) before premedication (1), 2 min before induction (2), 1 min after induction (3) and 1 min (4), 2 min (5) and 5 min (6) after intubation. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$ between placebo (○) and dexmedetomidine (●) groups.

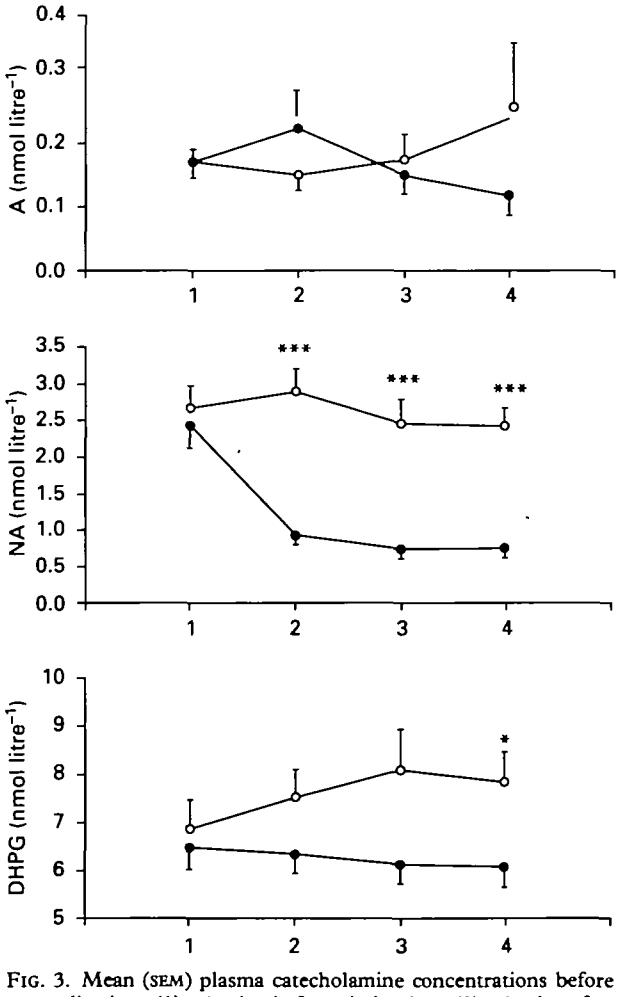

FIG. 3. Mean (SEM) plasma catecholamine concentrations before premedication (1), 1 min before induction (2), 1 min after induction (3) and 1 min after intubation (4). NA = Noradrenaline; A = adrenaline. *$P < 0.05$; ***$P < 0.001$ between placebo (○) and dexmedetomidine (●) groups.

significantly by dexmedetomidine compared with placebo ($P = 0.036$, t test). The maximum heart rate after intubation was 18% (CI 3–33%) less in the dexmedetomidine group (79 (SEM 6) beat min^{-1}) than in the placebo group (95 (5) beat min^{-1}) (fig. 1).

Dexmedetomidine induced relatively modest, but statistically significant decreases in systolic and diastolic arterial pressures at the time of induction ($P < 0.001$ for both, t test). The systolic and diastolic pressure maxima within 10 min after intubation also were smaller in the dexmedetomidine group ($P = 0.013$ and $P = 0.020$, t test) (fig. 1). The minimum and maximum pressure values during the operation were not significantly different between the groups. Patients in the dexmedetomidine group had smaller minimum ($P < 0.001$, t test) and maximum ($P = 0.038$, t test) diastolic and minimum systolic ($P < 0.001$, t test) arterial pressures in the postoperative period compared with those in the saline group (fig. 1).

Intraocular pressure

Dexmedetomidine induced a statistically significant decrease in IOP ($P = 0.013$, drug × time interaction in ANOVA) (fig. 2). Before induction, the decrease in IOP in the dexmedetomidine group was 34% (CI 27–43%) compared with the placebo group ($P < 0.001$, ANOVA). After intubation, the maximum IOP was 27% (CI 11–43%) smaller in the dexmedetomidine group than in the patients treated with placebo ($P = 0.005$, t test). Five minutes after intubation, the IOP were no longer significantly different between groups ($P = 0.077$, ANOVA).

Plasma catecholamine concentrations

Plasma concentrations of noradrenaline and one of its main metabolites, DHPG, measured as indicators of sympathetic nervous system activity, decreased significantly after administration of dexmedetomidine ($P < 0.001$ for both variables for drug × time interaction in ANOVA) (fig. 3). The plasma concentration of noradrenaline was decreased by 62% (CI 57–68%) before induction of anaesthesia. Induction of anaesthesia was associated with a small decrease in plasma noradrenaline concentration in both groups compared with preinduction values (fig. 3). Laryngoscopy and tracheal intubation did not cause any further increase in plasma catecholamine concentration, but plasma noradrenaline concentration remained smaller in the dexmedetomidine group, being only 31% of the noradrenaline concentration after placebo. The concentrations of adrenaline in plasma were low, and not significantly different between groups.

Anaesthetic requirements

The induction dose of thiopentone was significantly smaller (23%; CI 20–26%) in the dexmedetomidine group ($P = 0.012$, t test). In order to maintain heart rate and arterial pressure within the predetermined limits, additional supplements of isoflurane, fentanyl, or both, were needed more often in the saline group (table II). Isoflurane was used more often ($P = 0.037$, Fisher's exact test) in the placebo group. Although more fentanyl was administered in the placebo group, the difference was not statistically significant. Six patients (40%) in the placebo group needed both fentanyl and isoflurane, while in the dexmedetomidine group only one patient (7%) was treated with both agents ($P = 0.08$, Fisher's exact test).

Anaesthetic requirements are summarized in table II. The recovery time (response to verbal command after termination of nitrous oxide administration)

TABLE II. *Anaesthetic requirements (mean (SEM) or median (range))*

	Placebo ($n = 15$)	Dex. ($n = 15$)	P
Induction dose of thiopentone (mg)	315 (21)	242 (17)	0.012
Additional fentanyl (No. of patients)	8	3	0.128
Isoflurane administered (No. of patients)	10	4	0.037
Both fentanyl and isoflurane administered (No. of patients)	6	1	0.080
Duration of isoflurane administration (min)	17 (0–94)	0 (0–82)	0.018
Inspiratory isoflurane concentration (vol %)	0.20 (0–0.75)	0.0 (0–0.54)	0.031
Interventions during anaesthesia (No.)	3 (0–6)	0 (0–7)	0.040

was shorter in the dexmedetomidine group (118 (10) s) compared with placebo (156 (15) s) ($P = 0.042$, t test). After operation, two dexmedetomidine patients and one in the placebo group needed oxycodone in the recovery room.

DISCUSSION

We have found that a single i.v. dose of dexmedetomidine 0.6 $\mu g\ kg^{-1}$ effectively attenuated the increase in heart rate associated with laryngoscopy and tracheal intubation observed in the control group. Systolic and diastolic arterial pressures were also significantly less in the dexmedetomidine group. In addition, attenuated sympathetic activity was accompanied by decreases in plasma concentrations of noradrenaline (60–70 %) and one of its main metabolites, DHPG. Excessive bradycardia requiring treatment was not observed, not even in connection with the traction of extraocular muscles during surgery, the most common stimulus for the oculo–cardiac reflex [1]. However, all patients received glycopyrronium 4 $\mu g\ kg^{-1}$ and pancuronium, which has vagolytic effects.

Intraocular pressure

IOP is determined by extraocular muscle tone, scleral rigidity, vascularity of the orbit and production and outflow of aqueous humor [2, 4]. Dexmedetomidine prevented almost entirely the increase in IOP after laryngoscopy and tracheal intubation. The decrease in IOP was 34% after dexmedetomidine even before the adminstration of any other medication. After induction of anaesthesia with thiopentone, IOP decreased significantly in the placebo group also, but it returned to baseline values after laryngoscopy and tracheal intubation. The reduction in IOP induced by systemic administration of dexmedetomidine was of the same magnitude as that reported in a previous study with clonidine [9].

Thiopentone reduces IOP mainly via its depressant effect on the central diencephalic controlling areas for IOP, although increased aqueous drainage has also been shown to occur [2, 4]. Studies on the non-depolarizing neuromuscular blocking drug, pancuronium, have revealed either no effect or a decrease in IOP [2, 4]. Fentanyl is also known to reduce IOP [4]. The effect of nitrous oxide on IOP has received little attention [2], but it has been well established that all the volatile inhalation agents decrease IOP in a dose-dependent manner [2, 4]. Several mechanisms of action to alter IOP have been suggested: effects on the central controlling areas in the midbrain, by altering aqueous outflow and by altering extraocular muscle tone [2]. However, these inhalation agents may cause excessive cardiovascular depression, particularly in elderly patients, if concentrations are increased in an attempt to improve the ocular conditions for surgery.

Special attention was paid to intubation conditions during this study, so that the patients were fully paralysed (assessed by peripheral neurostimulator) before tracheal intubation, which was performed after standardized laryngoscopy (10 s). The intubation-induced increase in IOP was transient. Five minutes after intubation, there was no statistically significant difference between the groups.

Anaesthetic requirements

Clonidine has been shown to reduce the requirements for inhalation anaesthetics and opioids during coronary bypass surgery, in ophthalmic and gynaecological surgery [7, 9, 19]. This may be partly a result of analgesic properties, which have been verified after intrathecal, extradural and systemic administration [20, 21]. Dexmedetomidine has been shown to produce dose-dependent analgesia in animals [22], and its analgesic efficacy has recently been demonstrated in humans [23]. Dexmedetomidine has reduced the requirements for thiopentone and isoflurane in gynaecological surgery [13, 14]. Its hypnotic–anaesthetic action in the central nervous system appears to involve an inhibitory signal transduction protein, G_i-protein, which mediates the effect via increased conductance through a hyperpolarizing neuronal potassium channel [24].

In this study, the induction dose of thiopentone was also decreased significantly by dexmedetomidine, and the use of additional isoflurane and fentanyl supplementation for maintenance of anaesthesia was reduced in the dexmedetomidine group.

Sedation produced by dexmedetomidine after administration might have unblinded the clinician administering the anaesthetic agents. However, this probably did not affect the results, because the anaesthetic management was based on strict predetermined haemodynamic and clinical criteria.

In conclusion, we have shown that dexmedetomidine reduced IOP and attenuated the sympathoadrenal responses associated with laryngoscopy and intubation. It also reduced the requirements for thiopentone, opioid and inhalation anaesthetic agents. More extensive studies in elderly patients and in patients with increased IOP are warranted, to assess its value in routine management of ophthalmic anaesthesia.

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