Intramuscular Dexmedetomidine as Premedication for General Anesthesia

A Comparative Multicenter Study

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Background: Dexmedetomidine is a new potent and selective α_2-agonist that might prove useful as a preanesthetic agent.

Methods: A randomized, double-blind study design was used in 192 ASA physical status 1 and 2 patients scheduled for elective abdominal hysterectomy, cholecystectomy, or intraocular surgery under general anesthesia. Intramuscular injection of 2.5 µg/kg dexmedetomidine administered 60 min before and intravenous saline placebo 2 min before induction of anesthesia (DEXPLA group, n = 64) was compared with a combination of 0.08 mg/kg intramuscular midazolam 60 min and 1.5 µg/kg intravenous fentanyl 2 min before induction (MIDFENT group, n = 64), or a combination of intramuscular dexmedetomidine and intravenous fentanyl (DEXFENT group, n = 64). After thiopental induction, anesthesia was maintained with 70% N_2O/O_2, and fentanyl was administered according to clinical and cardiovascular criteria. Patients undergoing cholecystectomy received additional enflurane.

Results: Dexmedetomidine and midazolam induced comparable preoperative sedation and anxiolysis. The DEXFENT combination blunted the increases in blood pressure and heart rate induced by tracheal intubation more efficiently when compared with the DEXPLA and MIDFENT groups, in which approximately 25 mmHg and 15 beats/min greater increases were observed. The intraoperative fentanyl requirements were greater in MIDFENT patients when compared with both dexmedetomidine groups, in which 56% (DEXFENT group) and 31% (DEXPLA group) less fentanyl, respectively, was needed. Intraoperatively, fluids or vasopressors for hypotension and glycopyrrolate for bradycardia were administered more often to patients receiving dexmedetomidine than to those who did not. Postoperatively, there were no differences in oxygen saturation, analgesic, or antiemetic requirements, but dexmedetomidine-induced blood pressure and heart rate reductions were still evident at the end of the 3-h follow-up period. Bradycardia as an adverse event was reported more frequently in dexmedetomidine patients (20% in the DEXPLA and 33% in the DEXFENT groups) than in MIDFENT patients (8%).

Conclusions: The results suggest that pretreatment with a single intramuscular injection of 2.5 µg/kg dexmedetomidine is efficacious, but significantly increases the incidence of intraoperative hypotension and bradycardia in ASA physical status 1 or 2 patients. (Key words: Intubation, tracheal: sympathoadrenal response. Receptors: α_2-adrenergic. Sympathetic nervous system: α_2-adrenergic agonist; dexmedetomidine.)

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SEVERAL recent studies have shown the beneficial effects of α_2-agonists in anesthesiology. Perioperative activation of central α_2-adrenoceptors with clonidine, the prototype α_2-agonist, induces, *e.g.*, sedation, attenuation of sympathetic and cardiovascular responses to tracheal intubation, cardiovascular stability, potentiation of opioid and volatile anesthetics, reduction of intraocular pressure, and postoperative analgesia.[1]

Dexmedetomidine is a new potent and selective α_2-adrenoceptor agonist. Compared with clonidine, it is about 10-fold more selective toward the α_2-adrenoceptor and acts as a full agonist in most pharmacologic test models.[2,3,**] In preliminary clinical studies, dex-

medetomidine has been shown to decrease thiopental anesthetic requirements by up to 50% in patients undergoing cervical dilatation and curettage.[4,5] However, the duration of action of a single intravenous dexmedetomidine bolus may be sufficient only for minor surgical procedures. It has, therefore, become desirable to investigate other methods of administration to prolong the effect.

The aim of the study was to determine the efficacy and safety of intramuscular dexmedetomidine premedication in combined anesthesia, where thiopental, fentanyl, and nitrous oxide in oxygen were the principal anesthetic agents. Dexmedetomidine was compared with a standard anesthetic management, consisting of a combination of intramuscular midazolam and intravenous fentanyl.

Materials and Methods

Design

We performed a double-blind, randomized, multicenter (four operating units in three hospitals), and comparative study with three parallel groups (64 patients in each group):

1. a combination of intramuscular dexmedetomidine and intravenous saline placebo (DEXPLA group)
2. a combination of intramuscular dexmedetomidine and intravenous fentanyl (DEXFENT group)
3. a combination of intramuscular midazolam and intravenous fentanyl (MIDFENT group)

The protocol was approved by the ethics committees of the respective hospitals and submitted to the Finnish National Board of Health. Written, informed consent was obtained from each patient. The protocol-defined primary endpoints were preoperative sedation and anxiolysis, intubation responses, intraoperative cardiovascular variability, and anesthetic requirements (fig. 1).

Subjects

The study was carried out in 192 ASA physical status 1 and 2 patients between 19 and 65 yr of age scheduled for elective cholecystectomy, abdominal hysterectomy, or intraocular surgery under general anesthesia. Patients treated with clonidine or alphamethyl-dopa were excluded from the study. The sample size was based on a statistical power analysis (β = 0.2 and α = 0.05) using data from a separate pilot study,[6] *e.g.*, to find a
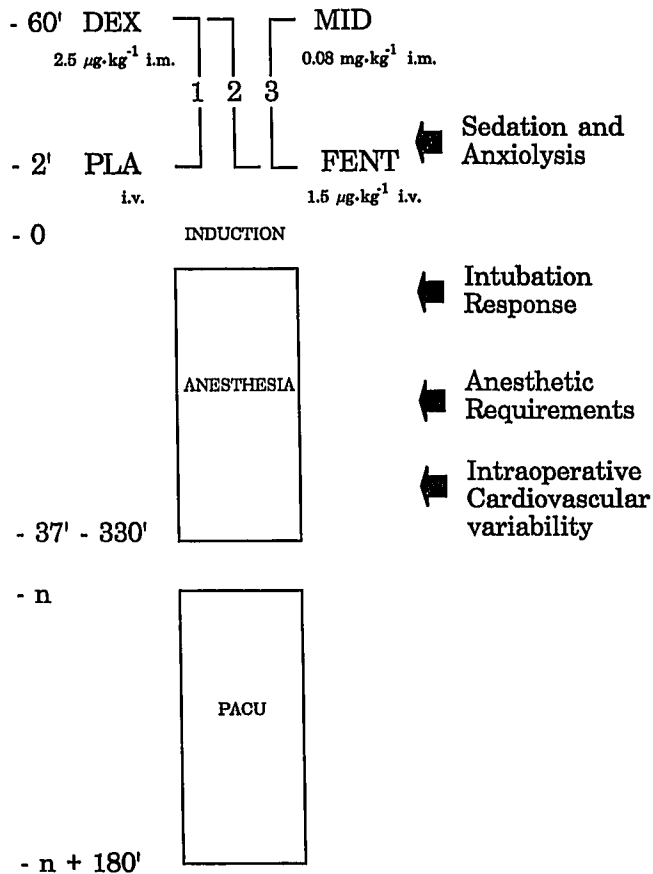

Fig. 1. Design and protocol-specified primary endpoints (response variables) of the study. 1 = DEXPLA; 2 = DEXFENT; 3 = MIDFENT. Differences in perioperative cardiovascular and blood oxygen saturation changes, numbers of intraoperative interventions, intra- and postoperative drug requirements, blood losses and recovery times, and adverse events between the three study groups also were assessed.

difference of one intraoperative fentanyl injection between groups.

The patients entered the hospital a day before the scheduled surgery and were interviewed and examined clinically as well as through routine laboratory testing.

Study Drugs and Randomization

Dexmedetomidine (2.5 μg/kg, Orion Corporation Farmos, Turku, Finland) or midazolam (0.08 mg/kg, Dormicum, Roche Pharmaceuticals, Basel, Switzerland) were given intramuscularly in the vastus lateralis muscle 60 min before anticipated induction of anesthesia. Fentanyl (1.5 μg/kg, Fentanyl, Orion Pharmaceutica, Espoo, Finland) or placebo (physiologic saline) were given *via* an intravenous cannula 2 min before the induction of anesthesia. If the administration of dexme-

detomidine or midazolam was not performed between 45 and 90 min before induction, the patient was excluded from the efficacy analyses.

Because midazolam and fentanyl were in commercial dosage forms, the double-blind nature of the study was ensured by having a nurse not participating in the study responsible for the study drug preparations in each hospital. The nurse injected the intramuscular drugs and prepared the intravenous drugs into a ready-to-use form by drawing it into a 5-ml syringe and diluting it into a 5-ml volume with physiologic saline.

Stratified balanced randomization was used with randomly permuted blocks within strata. The type of surgery was used to divide the patients into three strata.

Study Procedure and Measurements

Before administration of the intramuscular study drug, each patient's systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) were measured in the operating unit to determine the baseline values (to which values during anesthesia were compared). The 100-mm visual analog scales for sedation ("alert–sleepy") and anxiety ("excited–calm") were completed by each patient immediately before administration of the intramuscular study drug. A dorsal vein of the right hand was cannulated, and an intravenous infusion was started. All patients received 100–200 ml 2.5% dextrose in half-normal saline before induction of anesthesia. Before transfer to the operating room, the visual analog scales were completed again by each patient.

In the operating room, 2 min before induction of anesthesia, fentanyl or saline placebo was given via an intravenous cannula (volume 5 ml). At the same time, all patients received 0.2 mg intravenous glycopyrrolate (Gastrodyn, Leiras, Turku, Finland).

Electrocardiographic lead V$_5$ was monitored throughout the preinduction, induction, intraoperative, and postoperative periods. Systemic blood pressure was measured at 1-min intervals until 10 min after intubation, at 5-min intervals intraoperatively, and at 15-min intervals postoperatively with an automated oscillometric device (Sphygmomanometer BP-103N mark III, Nippon Colin, Tokyo, Japan, or Cardiocap, Datex Instrumentarium, Helsinki, Finland). Arterial hemoglobin oxygen saturation was monitored transdermally and recorded at 5-min intervals intraoperatively and at 15-min intervals postoperatively using a SatLite Plus pulse oximeter (Datex Instrumentarium). To assess the intraoperative cardiovascular variability, coefficients of

variation for BP and HR were calculated by using the following formula:

$$\frac{\text{SD of intraoperative values}}{\text{Mean of intraoperative value}} \times 100.$$

The end-tidal carbon dioxide concentration was monitored continuously using capnometric device (Cardiocap). Muscle relaxation was monitored with a peripheral nerve stimulator.

Anesthesia

After breathing oxygen for 3 min via face mask, anesthesia was induced with 4 mg/kg sodium thiopental (Hypnostan, Leiras, Finland) over 30–45 s. The initial dose was supplemented with 1-mg/kg incremental doses, if clinically required. The patients' lungs were then manually ventilated with 100% O$_2$.

Muscle relaxation was achieved with succinylcholine (Sukolin, Orion Pharmaceutica) 1.5 mg/kg and maintained with vecuronium (Norcuron, Organon, Oss, The Netherlands), an initial 0.1-mg/kg bolus with subsequent 0.03-mg/kg incremental boluses when the first twitch in a train-of-four response was observed.

After tracheal intubation, mechanical ventilation was started and anesthesia maintained with 70% N$_2$O/O$_2$, and fentanyl was administered as required to meet the predetermined endpoints of anesthetic management (see below). All patients undergoing cholecystectomy received supplemental enflurane (Efrane, Abbott, Campoverde, Italy) at a fixed 0.4% end-tidal concentration (Capnomac, Datex Instrumentarium, Helsinki, Finland). In these patients, the enflurane administration was started 2–5 min before the first surgical incision.

From 10 min after intubation, tachycardia (30% increase from baseline or >90 beats/min), hypertension (20% increase or >180 mmHg), and signs of insufficient anesthesia (e.g., lacrimation, sweating and flushing) were treated with 2-μg/kg intravenous bolus doses of fentanyl. If hypotension (30% decrease from baseline or <80 mmHg) occurred, 250 ml of Ringer's lactate over 5 min first was administered. If this was insufficient or the decrease was profound (SBP <70 mmHg) or rapid with tachycardia, etilefrine (Effortil, Boehringer Ingelheim, Ingelheim am Rhein, Germany), a sympathomimetic amine with α- and β_1-agonist properties,[7] was administered in 3-mg intravenous increments. Bradycardia (HR <45 beats/min) was treated with a bolus injection of 0.2 mg intravenous glycopyrrolate. Fluid challenges, additional thiopental, fentanyl, etilefrine, and glycopyrrolate injections were considered

as interventions to achieve the endpoints of anesthetic management.

To maintain arterial hemoglobin oxygen saturation greater than 90%, the fraction of inspired oxygen was allowed to vary between 0.30 and 0.35. Controlled mechanical ventilation with a tidal volume of 10 ml/kg was adjusted to maintain end-tidal carbon dioxide tension between 30 and 35 mmHg (4.5–5.5 kPa).

During the operation, 2.5% dextrose in half-normal saline infusion was administered as the maintenance fluid at a rate of 6–8 ml $\cdot$ kg^{-1} $\cdot$ h^{-1}. Blood loss less than 500 ml was replaced with 200 ml of Ringer's lactate for each 100 ml of blood, and thereafter with 200 ml of Ringer's lactate and 100 ml of 6% hydroxyethyl starch (Plasmafusin, Leiras, Finland) for each 100 ml of blood. If blood loss was greater than 1,000 ml, the patient was excluded from the efficacy analyses.

In patients undergoing cholecystectomy, enflurane was discontinued when peritoneal closure was commenced. After skin closure, the residual neuromuscular block was reversed with 0.5 mg glycopyrrolate and 2.5 mg neostigmine (Robinul-Neostigmine, Robins, West Sussex, United Kingdom), and nitrous oxide was discontinued.

Postoperative Follow-up

The patient was allowed to breathe 100% O_2 until transferred to the postanesthesia care unit, where oxygen (fraction of inspired oxygen 0.28) was delivered through a Ventimask (Vickers Medical, Hampshire, United Kingdom). The patient was monitored in the postanesthesia care unit until there were no signs of any drug-induced adverse effects (e.g., excessive tiredness, hypotension) and for at least 3 h. Oxycodone (Oxanest, Leiras) was administered intravenously in 3-mg increments to control postoperative pain, and metoclopramide (Metopram, Leiras) at 10-mg intravenous increments for postoperative nausea. Postoperative respiratory depression was treated primarily by verbally stimulating the patient and instructing him/her to breathe deeply a few times. If this was insufficient, 0.5 mg/kg intravenous doxapram (Dopram, Robins) was administered, followed by 0.25-mg/kg increments if clinically required to maintain acceptable respiration.

Adverse Events

All subjective and objective adverse events were recorded and assessed by the investigator on a three-grade scale (1 = mild, 2 = moderate, and 3 = severe). Patients underwent only routine laboratory testing preopera- tively. In a subgroup of 36 patients, basic hematologic laboratory tests were performed postoperatively also.

Statistical Analyses

The use of parametric or nonparametric test for a particular response variable was decided after examining the normality of the residuals. If differences among the treatment groups were revealed by an overall test, contrasts were applied to indicate the significance of pairwise comparisons. Ninety-five-percent Bonferroni corrected confidence intervals (95% CI) were computed for the treatment differences in primary response variables.

The homogeneity of the treatment groups with respect to the demographic factors were examined using two-way analysis of variance. Likelihood ratio test was applied in testing sex, and logistic regression analysis was performed for previous diseases and previous or concomitant medication.

Sedative and anxiolytic effects, intubation responses (i.e., maximal increases in SBP and HR), changes in SBP and HR, cardiovascular variability (as coefficients of variation), total number of interventions and blood loss, and arterial hemoglobin oxygen saturation were tested using two-way (treatment, type of surgery) and three-way (treatment, type of surgery, time) analysis of covariance, or two-way (treatment, type of surgery or time) analysis of variance. Pre-, intra-, and postoperative periods were analyzed separately to characterize the time dependency of the observed effects in more detail.

To identify any increase in the need of additional thiopental or fentanyl, logistic regression analysis was performed for the number of patients who needed additional drug. Two-way analysis of variance was performed for the total amount of drug. The same tests were used for other intra- and postoperative drug requirements. The distribution of recovery time (i.e., time from discontinuation of nitrous oxide until extubation), duration from intramuscular study drug administration until induction, duration of anesthesia, and duration of surgery were estimated with product-limit method. Cox's proportional hazard model was used to identify the differences among the study groups. Because of small counts, generalized Fisher's exact test was used to identify differences among the groups in the number of patients with adverse events and in the number of patients with low SBP and HR values.

The statistical analyses were done using Statistical Analysis Software (SAS Institute, Cary, NC) and BMDP

Table 1. Summary of the Demographic Patient Characteristics

Demographic Factor	DEXPLA	DEXFENT	MIDFENT	P
No. of patients: (hysterectomy + cholecystectomy + intraocular = total)	39 + 14 + 10 = 63	39 + 14 + 10 = 63	38 + 14 + 9 = 61	
Age (yr)	44 ± 10	44 ± 9	43 ± 10	0.9
Weight (kg)	72 ± 12	73 ± 12	69 ± 11	0.02
Height (cm)	166 ± 8	168 ± 9	165 ± 7	0.02
Sex (female/male)	54/9	51/12	53/8	0.6
Systolic blood pressure (mmHg)	133 ± 18	131 ± 17	131 ± 18	0.9
Diastolic blood pressure (mmHg)	79 ± 13	78 ± 11	76 ± 11	0.4
Heart rate (beats/min)	73 ± 11	71 ± 10	72 ± 11	0.8
Previous and concomitant medication (no. of patients)	23 (37%)	15 (24%)	18 (30%)	0.5
Previous diseases (cardiorespiratory + gastrointestinal + neurologic + other = total) (no. of patients)	10 + 6 + 3 + 6 = 25	8 + 4 + 5 + 6 = 23	10 + 3 + 3 + 12 = 28	0.2

Values are mean ± SD. DEXPLA = dexmedetomidine and placebo; DEXFENT = dexmedetomidine and fentanyl; MIDFENT = midazolam and fentanyl.

(BMDP Statistical Software, Los Angeles, CA) statistical software in a VAX 3100/VMS computer (Orion Corporation Farmos; J.T.). When nonparametric tests were used, the median and quartile deviation is given instead of mean and standard deviation or standard error.

Results

Patient Inclusion and Surgery

One hundred ninety-two patients, 64 in each group, were included in the study. One hundred twenty patients underwent hysterectomy, 42 cholecystectomy, and 30 intraocular surgery. Four patients were excluded from the efficacy analyses because of a delay (more than 90 min) between premedication and induction, and one patient because of excessive (more than 1,000 ml) blood loss during hysterectomy. Thus, 187 patients (158 women and 29 men) were evaluated for efficacy and 192 for safety.

There were slight but statistically significant differences among groups in weight and height. Otherwise, the patient groups were comparable with respect to the selected demographic (table 1), preoperative laboratory tests (data not shown) and operational (table 2) factors. Only six patients suffered from mild hypertension, and three were treated with β-blocking agents. Blood loss during hysterectomy and cholecystectomy was similar in all groups (192, 193, and 244 ml in the DEXPLA, DEXFENT, and MIDFENT groups, respectively; NS). Type of surgery did not have any impact on efficacy or safety results.

Preoperative Sedation and Anxiolysis

The degrees of sedation and anxiety before premedication were comparable in all groups. A clear increase in sedation and a moderate decrease in anxiety were seen in all groups (fig. 2), and there were no statistically significant differences among the groups ($P = 0.07$ for sedation and $P = 0.07$ for anxiolysis).

Table 2. Summary of Operational Factors

Operational Factor	DEXPLA	DEXFENT	MIDFENT	P
Duration from intramuscular study drug until induction (min)	60 ± 8	58 ± 7	57 ± 8	0.9
Duration of anesthesia (min)	117 ± 19	108 ± 16	113 ± 18	0.8
Duration of surgery (min)	100 ± 23	90 ± 20	97 ± 39	0.8
Time to extubation (s)	90 ± 38	85 ± 68	80 ± 41	0.5
Total amount of liquids (ml)	1,670 ± 570	1,650 ± 580	1,510 ± 570	0.06
Blood loss (ml)	192 ± 127	193 ± 147	244 ± 184	0.7

Data are medians or means ± SD (liquids and blood loss); blood loss data are from hysterectomy and cholecystectomy patients.

DEXPLA = dexmedetomidine and placebo; DEXFENT = dexmedetomidine and fentanyl; MIDFENT = midazolam and fentanyl.
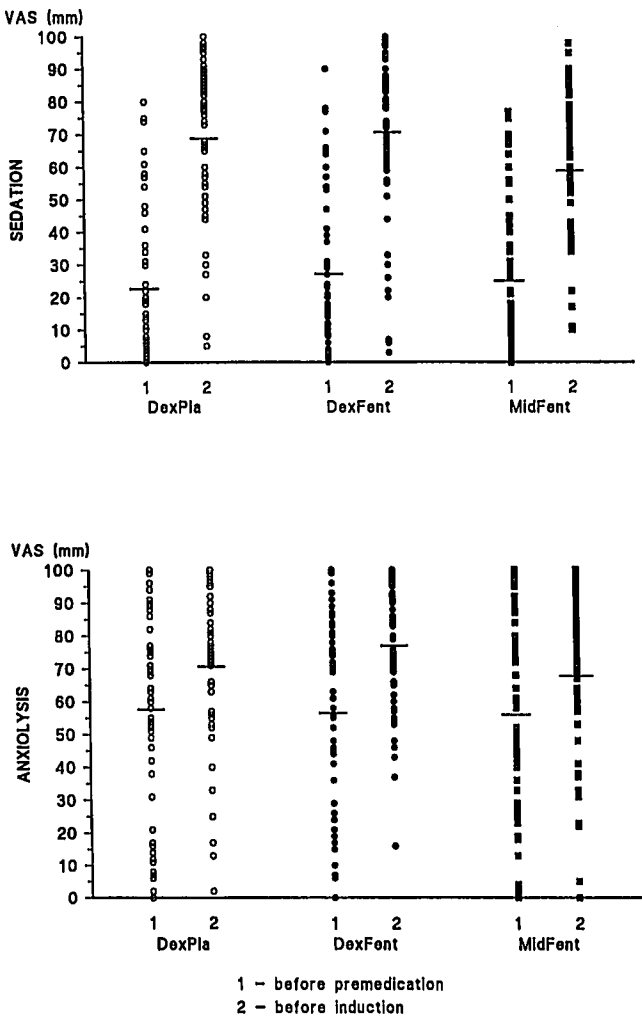
Fig. 2. Individual visual analog scales for preoperative sedation and anxiolysis. Crossed lines indicate the mean values of the responses. No statistically significant differences between the groups. Ninety-five-percent confidence intervals for the changes within the study groups were 37–54, 38–55, and 29–46 mm for sedation, and 9–25, 14–30, and 6–22 mm for anxiolysis in the DEXPLA, DEXFENT, and MIDFENT groups, respectively.

Intubation Responses and Other Cardiovascular Effects

Baseline SBP and HR values were comparable in all groups. Preoperatively, dexmedetomidine induced moderate but statistically significant decreases in SBP ($P < 0.001$), DBP ($P = 0.001$), and HR ($P = 0.001$). Compared with the MIDFENT group, SBP values were on average 10–14 mmHg, DBP 6 mmHg, and HR 8

beats/min lower in the DEXPLA and DEXFENT groups 5 min before induction of anesthesia (fig. 3).

Tracheal intubation induced modest increases of SBP and HR in the DEXPLA and MIDFENT groups, whereas in the DEXFENT group, no increase (SBP) or only a slight increase (HR) from baseline was observed. The highest individual adjusted mean (SE) SBP and HR values from induction until 10 min after intubation were 156 (3), 130 (3), and 153 (4) mmHg, and 92 (2), 78 (2), and 94 (2) beats/min in the DEXPLA, DEXFENT, and MIDFENT groups, respectively, the differences among groups being statistically significant ($P < 0.001$ for SBP and $P < 0.001$ for HR; fig. 3). The 95% CIs for differences between the DEXFENT and DEXPLA groups were 16–36 mmHg and 7–21 beats/min, and between the DEXFENT and MIDFENT groups 12–33 mmHg and 9–23 beats/min, for SBP and HR, respectively. The DEXPLA and MIDFENT groups did not differ significantly from each other.

Intraoperatively, transient initial decreases were seen in BP and HR in all groups. After reaching a plateau within 30 min from intubation, SBP values were in average 15 mmHg, DBP 10 mmHg, and HR 10–5 beats/min lower in the dexmedetomidine groups compared with the MIDFENT group (fig. 3). The differences among the groups were statistically significant ($P < 0.001$ for SBP, $P = 0.001$ for DBP, $P = 0.001$ for HR). Mean SBP remained less than baseline in the dexmedetomidine groups, whereas a slight increase was observed in the MIDFENT group. The intraoperative coefficients of variation for SBP, DBP, and HR were comparable in all groups, varying between 10.1 and 14.4%.

In the postanesthesia care unit, the mean SBP, DBP, and HR were approximately 13% less in both dexmedetomidine groups when compared with the MIDFENT group (fig. 3). Statistical analyses revealed significant differences ($P < 0.001$) among the study groups. No symptomatic hypotension or bradycardia was observed.

Respiratory Measurements

Arterial hemoglobin oxygen saturation values varied similarly in all groups during the intra- and postoperative periods, and there were no statistically significant differences among the groups (data not shown). The lowest individual value in the postanesthesia care unit was 95 in all three groups. Only seven patients (one in the DEXPLA, three in the DEXFENT, and three in the MIDFENT group) had arterial hemoglobin oxygen saturation values ≤90% ($P = 0.7$).

Fig. 3. Perioperative mean values of systolic blood pressure (SBP) and heart rate (HR) recorded at 1-min intervals from induction until 10 min after intubation, at 5-min intervals (or more often if necessary) intraoperatively, and at 15-min intervals in the postanesthesia care unit. Intubation responses for SBP and HR are presented as barcharts in separate panels. Baseline (open bars) and individual maximums (hatched bars) from induction until 10 min after intubation are displayed.
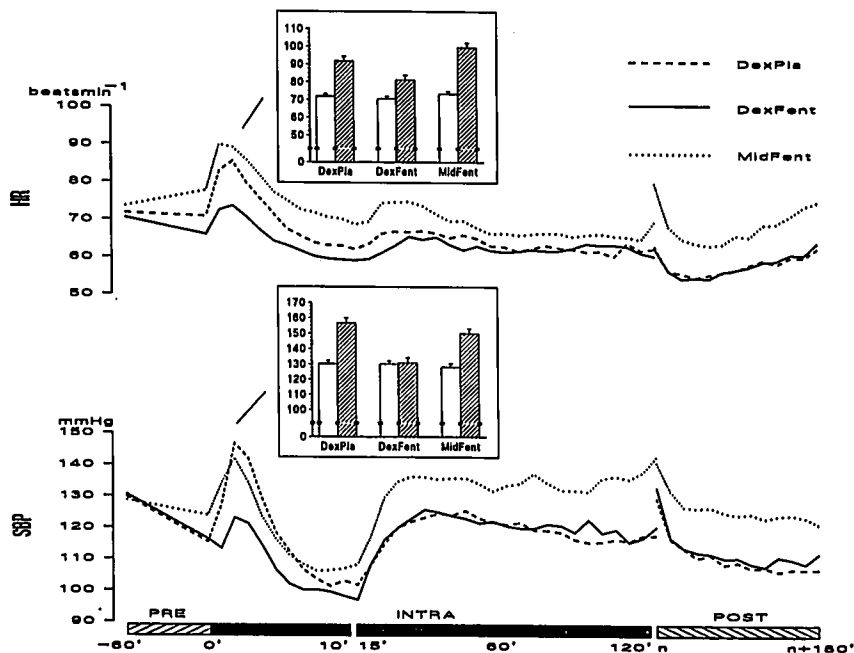
Anesthetic Requirements and Interventions

. Additional thiopental was given to 28 patients (15%) for induction of anesthesia. Eighty-six percent of all patients required supplemental fentanyl to meet the endpoints of anesthetic management. The average total amount (per patient weight and duration of surgery) of required fentanyl was greater in MIDFENT patients ($P < 0.001$). DEXFENT patients required 56% (95% CI 26–87%), and DEXPLA 31% (95% CI 1–63%) less fentanyl than MIDFENT patients (table 3).

Ten patients required volatile anesthetic (isoflurane or enflurane) for persistent hypertension/tachycardia in addition to protocol-defined anesthetics. In addition, 12 patients undergoing cholecystectomy were acci-

dentally given enflurane slightly more than the protocol allowed (0.4% end-tidal). Two patients were given additional thiopental at the end of surgery. There were no significant differences in the need for additional anesthetics among the study groups.

To meet the predetermined hemodynamic endpoints, dexmedetomidine treated patients received fluid boluses ($P < 0.001$ among groups) and etilefrine ($P = 0.05$) for hypotension and glycopyrrolate ($P < 0.001$) for bradycardia more frequently than MIDFENT patients. In addition, atropine was given to two dexmedetomidine-treated patients. The adjusted mean number of interventions was 3.5 (SE 0.3), 3.2 (SE 0.3)m and 3.1 (SE 0.3) in the DEXPLA, DEXFENT, and

Table 3. Summary of Intraoperative Drugs and Total Number of Interventions to Meet the End Points of Anesthetic Management

	DEXPLA		DEXFENT		MIDFENT		P
Protocol-specified drugs							
Thiopental (no. of patients)	12	(19%)	5	(8%)	11	(18%)	0.1
Fentanyl (no. of patients)	57	(91%)	46	(73%)	57	(93%)	<0.001
Total amount ($\mu g \cdot kg^{-1} \cdot h^{-1}$) (SE)	2.2 (0.3)		1.4 (0.3)		3.2 (0.3)		<0.001
Fluid challenge (no. of patients)	25	(40%)	34	(54%)	7	(12%)	<0.001
Etilefrine (no. of patients)	6	(10%)	5	(8%)	0	(0%)	0.05
Glycopyrrolate (no. of patients)	23	(37%)	27	(43%)	8	(13%)	<0.001
Total no. of interventions (SE)	3.5 (0.3)		3.2 (0.3)		3.1 (0.3)		0.6
Additional volatile anesthetics (no. of patients)	2	(3%)	3	(5%)	5	(8%)	0.4

Except for fentanyl, there were no statistically significant differences in the amounts of drugs administered.

DEXPLA = dexmedetomidine and placebo; DEXFENT = dexmedetomidine and fentanyl; MIDFENT = midazolam and fentanyl.

Table 4. Summary of Postoperative Drugs

	DEXPLA	DEXFENT	MIDFENT	P
Protocol-specified drugs (no. of patients)				
Doxapram	3 (5%)	6 (10%)	6 (10%)	0.4
Oxycodone	57 (91%)	55 (87%)	56 (92%)	0.6
Metoclopramide	14 (22%)	19 (30%)	20 (33%)	0.4
Additional drugs (no. of patients)				
NSAIDs	5 (8%)	3 (5%)	5 (8%)	0.8
Droperidol	3 (5%)	2 (3%)	2 (3%)	1.0
Fluids or etilefrine	1 (2%)	2 (3%)	0 (0%)	0.8
Other drugs	1 (2%)	1 (2%)	1 (2%)	1.0

There were no statistically significant differences in the amounts of drugs administered.

DEXPLA = dexmedetomidine and placebo; DEXFENT = dexmedetomidine and fentanyl; MIDFENT = midazolam and fentanyl.

MIDFENT groups, respectively (NS). All intraoperative drug interventions are summarized in table 3.

Recovery and Postoperative Follow-up

Time from nitrous oxide termination until extubation was similar in all groups (NS; table 2). Fifteen patients were given doxapram for postoperative ventilatory depression, and there were no statistically significant differences among the groups (table 4). One MIDFENT patient received naloxone also.

One hundred sixty-eight (90%) patients, *i.e.*, 57 (91%) in the DEXPLA, 55 (87%) in the DEXFENT, and 56 (92%) in the MIDFENT group required oxycodone for postoperative pain (NS). In addition to the protocol-defined analgesic, nonsteroidal antiinflammatory drugs (usually ketoprofen or diclofenac) were given to 13 patients. There were no statistically significant differences among the study groups in the use of analgesics, antiemetics or other drugs (table 4).

Safety

Thirty-two (50%) patients in the DEXPLA, 37 (58%) in the DEXFENT, and 28 (44%) patients in the MIDFENT group had adverse events (NS; table 5). The numbers of single events were 57, 56, and 44, respectively. Bradycardia was reported as an adverse event more frequently in the dexmedetomidine patients (13 patients in the DEXPLA and 21 in the DEXFENT group) compared with only five patients in the MIDFENT group ($P = 0.002$). Hypotension was reported as an adverse event in five dexmedetomidine patients (one in the DEXPLA and four in the DEXFENT group) and none in the MIDFENT group ($P = 0.1$). Otherwise, the adverse events and their profile of severity were comparable in all groups (table 5). All adverse events were transient.

In the DEXPLA group, one previously healthy patient had severe bradycardia before induction of anesthesia with a lowest value of 35 beats/min. The patient lost consciousness for 2 min while three consecutive automated recordings failed to measure BP. Three milligrams etilefrine was administered intravenously, and the condition restored immediately before the investigator had atropine ready for injection. The patient received one glycopyrrolate injection (HR 42 beats/min) also in the postanesthesia care unit, but otherwise the surgery and recovery was uneventful.

Postoperative laboratory tests were performed in 36 (12 per group) hysterectomy cases without clinically abnormal individual changes from preoperative values or differences among the groups (data not shown). Pain or irritation of the injection sites was not reported.

Discussion

The major finding of this study was that a single intramuscular injection of 2.5 μg/kg dexmedetomidine administered 1 h before induction of general anesthesia

Table 5. Summary of Adverse Events

Adverse Event (AE) (No. of Patients)	DEXPLA	DEXFENT	MIDFENT	P
With AE(s)	32 (50%)	37 (58%)	28 (44%)	0.3
With severe AE	2 (3%)	0 (0%)	3 (5%)	0.4
Bradycardia	13 (20%)	21 (33%)	5 (8%)	0.002
Hypotension	1 (2%)	4 (6%)	0 (0%)	0.1
Emesis, nausea, or vomiting	20 (31%)	16 (25%)	20 (31%)	0.7
Other	1 (2%)	4 (6%)	5 (8%)	0.4

DEXPLA = dexmedetomidine and placebo; DEXFENT = dexmedetomidine and fentanyl; MIDFENT = midazolam and fentanyl.

is an effective anesthetic adjunct, but possesses significant cardiovascular activity, manifesting in increased perioperative bradycardia and hypotension in healthy ASA physical status 1 and 2 patients.

Growing interest for use of α_2-adrenoceptor agonists in anesthesia has emerged during the past 5 yr.[1] Clonidine has been shown to decrease the sympathetic and cardiovascular responses to laryngoscopy, tracheal intubation, and surgical stress,[8,9] to decrease the need for volatile and opioid anesthetics during surgery,[8,10] and to decrease hemodynamic variability.[10] It also may alleviate postoperative pain after systemic and epidural administration.[11]

Dexmedetomidine is a potent α_2-agonist that decreases halothane anesthetic requirements to the extent that it may act as an anesthetic by itself at high doses.[12,13] This effect is mediated by central α_2-adrenoceptors coupled to a pathway involving pertussis toxin sensitive inhibitory guanosine triphosphate-binding proteins and activation of potassium channels, resulting in neuronal cell membrane hyperpolarization.[12,14] Recent data suggest that the locus coeruleus is the key anatomic site for hypnotic-anesthetic actions of α_2-agonists.[15]

The present results agree with previous dexmedetomidine studies in which the drug usually was given intravenously. A 0.6-μg/kg intravenous bolus, administered 10 min before induction, blunted the hemodynamic responses to laryngoscopy and tracheal intubation, as well as attenuated the plasma norepinephrine increases.[16,17] By combining dexmedetomidine and the opioid, superior efficacy in blunting the intubation response to standard pretreatment was accomplished in the present study. In contrast to earlier experience,[4,5,16–18] dexmedetomidine did not decrease the induction dose of thiopental in our study. We applied, however, a relatively high initial dose (4 mg/kg), which accounts for the discrepancy.

Recently, 0.6 μg/kg intravenous dexmedetomidine was reported to reduce the isoflurane requirements by approximately 25% during general anesthesia.[19] In the present study, 2.5 μg/kg intramuscular dexmedetomidine decreased the need for intraoperative fentanyl by approximately 60%. Whether this was due to a true anesthetic potentiation is impossible to say, because fentanyl administration was titrated primarily according to cardiovascular criteria and dexmedetomidine itself possesses hemodynamic activity. Neither can we exclude the possibility for a pharmacokinetic interaction, because we did not measure plasma concentrations

of fentanyl. In a recent study in which anesthesia was maintained with continuous alfentanil infusion, clonidine increased plasma alfentanil concentrations by 60%.[20]

Dexmedetomidine also has analgesic activity,[21] which may have clinical implications. Opioid potentiation or analgesic effects were not seen as reductions of postoperative analgesic requirements in the present study. The follow-up time was too short, however, and the analgesic treatment scheme not optimal to properly assess this question. Perioperative clonidine administered transdermally until 48 h postoperatively has been shown to reduce postoperative morphine requirements by 40–50%.[20] Also, dexmedetomidine has been shown to alleviate pain after laparoscopic tubal ligation, but at a dose level that simultaneously increased the likelihood of sedation and bradycardia.[22]

High plasma concentrations of α_2-agonists induce vasoconstriction due to activation of postjunctional α_2-adrenoceptors in vascular smooth muscle,[23] resulting in blood pressure increases.[24,25] This potentially harmful phenomenon restricts the use of large bolus doses of intravenous dexmedetomidine even for relatively short procedures in which anesthetic potentiation tends to lessen and disappear.[19] Indeed, in a recent study, where dexmedetomidine was administered as a constant infusion throughout the surgery, isoflurane requirements were diminished by more than 90%.[26] The intramuscular route, which enabled a larger bolus dose without the initial hypertensive phase, was selected for the present study to prolong the effects of dexmedetomidine[27] in a more practical way.

The 2.5-μg/kg dose was based on a dose-finding study by Aho et al.,[28] and it indeed turned out to be comparably sedative and anxiolytic to 0.08 mg/kg midazolam. In another recent study, an intramuscular dexmedetomidine dose of 1.0 μg/kg was somewhat less sedative than 0.08 mg/kg midazolam before minor gynecologic surgery.[18] The maximal psychomotor impairment in healthy human subjects was slightly greater after 0.08 mg/kg intramuscular midazolam than after dexmedetomidine 1.2 μg/kg, but the effects lasted longer with the latter.[29] Dexmedetomidine induces dose-dependent impairment of vigilance—without reasonable doubt—but anxiolytic properties in clinical situations need further evidence. The limitations concerning the design of our study are evident, and a placebo-controlled study is warranted to demonstrate the possible preoperative anxiolytic efficacy of dexmedetomidine. Interestingly, dexmedetomidine and mida-

zolam have been shown to possess synergistic hypnotic effects through a pharmacodynamic interaction.[30]

The cardiovascular stabilization effect with α_2-agonists is of special interest to clinical anesthesiologists.[31] Clonidine has been shown to reduce intraoperative BP and HR variability,[8,10,20] but negative results also have been obtained in controlled studies.[32] Dexmedetomidine did not stabilize hemodynamics in the present study partly because of the selected population, *i.e.*, healthy normotensive patients, but mainly because of the study design. A negative result in coefficients of variation serves as a quality assurance for protocol adherence, *i.e.*, the predetermined endpoints of anesthetic management were achieved in the present study. Nevertheless, the possible cardiovascular stabilization effect of dexmedetomidine should be investigated in hypertensive (hyperkinetic) patients undergoing vascular or other major surgery.

The cardiovascular effects of α_2-agonists may limit their general use in anesthesia practice. The incidence of hypotension and bradycardia and subsequent need for interventions were increased despite glycopyrrolate prophylaxis in the present study. Whether a larger or repeated dosage of glycopyrrolate would have been more effective remains to be studied. Our selection of concomitant drugs also may have contributed to the results. Vecuronium and fentanyl are well known for their propensity to cause bradycardia. High incidences of perioperative hypotension and bradycardia have been reported with clonidine,[32,33] and caution has been suggested in its use as a premedicant.[33] Although these untoward effects respond to adequate treatment, the three- to fivefold increase in the need for vagolytics and liquids/pressors observed in the present study overweighs the efficacy benefits, at least in healthy patients.

Postoperative manifestations of cardiovascular problems could be overcome, due to the receptor specific mechanism of action, by introduction of an antagonist. Atipamezole, a highly specific and selective α_2-antagonist,[34,35] has been demonstrated to rapidly and effectively reverse the cardiovascular and sedative effects of dexmedetomidine in healthy human subjects.[36] Preliminary results indicate that intravenous atipamezole may shorten the psychomotor impairment after dexmedetomidine-induced sedation in patients recovering from a short gynecologic procedure.[37] This restraint-reversal concept with specific and selective α_2-adrenergic drugs already is used in veterinary practice.[38]

The heterogeneity of α_2-adrenoceptors and regional differences in the distributions of the distinct subtypes in the central nervous system[39,40] increase further the attractiveness of this class of drugs. Different α_2-adrenoceptor subtypes may have distinct physiologic functions in human brain, opening new perspectives for modern anesthesiology. The ongoing characterization and localization of α_2-adrenoceptor subtypes together with rational drug design augur well for future introduction of new potent agonists targeted specifically to the α_2-receptor subtype responsible for anesthetic action but, perhaps, without activity toward subtypes responsible for the unwanted cardiovascular effects.[41]

Though preoperative sedation and anxiolysis, attenuation of intubation responses, and reduction of intraoperative opioid requirements were achieved with a single intramuscular injection of 2.5 μg/kg dexmedetomidine, the high incidence of intraoperative hypotension and bradycardia suggests caution in its perioperative use.

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