

Anesthesiology  
78:1065-1075, 1993  
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## Intramuscular Dexmedetomidine as Premedication for General Anesthesia

### A Comparative Multicenter Study

Harry Scheinin, M.D.,\* Marja-Leena Jaakola, M.D.,† Sari Sjövall, M.D.,‡ Timo Ali-Melkkilä, M.D.,†  
Seppo Kaukinen, M.D.,§ Jari Turunen, M.Sc.,|| Jussi Kanto, M.D.#

**Background:** Dexmedetomidine is a new potent and selective  $\alpha_2$ -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  $\mu\text{g}/\text{kg}$  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  $\mu\text{g}/\text{kg}$  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%  $\text{N}_2\text{O}/\text{O}_2$ , 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  $\mu\text{g}/\text{kg}$  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:  $\alpha_2$ -adrenergic. Sympathetic nervous system:  $\alpha_2$ -adrenergic agonist; dexmedetomidine.)

\* Anesthesia Resident; Assistant Professor of Pharmacology Department of Anesthesiology, Turku University Central Hospital, Turku, Finland. At the time this study was performed, Dr. Scheinin was an employee of Orion Corporation Famos. Currently, Dr. Scheinin acts as a consultant to Orion Corporation Famos.

† Staff Anesthesiologist, Department of Anesthesiology, Turku University Central Hospital.

‡ Staff Anesthesiologist, Regional Hospital of Rauma.

§ Chief Anesthesiologist; Assistant Professor of Anesthesiology, Department of Anesthesiology, Tampere University Hospital.

|| Biostatistician, Orion Corporation Famos.

# Professor of Anesthesiology, Department of Anesthesiology, Turku University Central Hospital.

Received from the Departments of Anesthesiology and Clinical Pharmacology, Turku University Central Hospital, Turku, Finland; Regional Hospital of Rauma, Rauma, Finland; Department of Anesthesiology, Tampere University Hospital, Tampere, Finland; and Orion Corporation Famos, Research Center, Turku, Finland. Accepted for publication March 11, 1993. Supported by Orion Corporation Famos, Research Center, Turku, Finland.

Address reprint requests to Dr. Scheinin: Department of Anesthesiology, Turku University Central Hospital, Klännylynkatu 4-8, SF-20520 Turku, Finland.

\*\* Savola J-M, Roberts JM: Dexmedetomidine is more efficacious than clonidine as an  $\alpha_2$ -agonist in human platelet membranes (abstract). FASEB J 3:A836, 1989.

SEVERAL recent studies have shown the beneficial effects of  $\alpha_2$ -agonists in anesthesiology. Perioperative activation of central  $\alpha_2$ -adrenoceptors with clonidine, the prototype  $\alpha_2$ -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.<sup>1</sup>

Dexmedetomidine is a new potent and selective  $\alpha_2$ -adrenoceptor agonist. Compared with clonidine, it is about 10-fold more selective toward the  $\alpha_2$ -adrenoceptor and acts as a full agonist in most pharmacologic test models.<sup>2,3,\*\*</sup> In preliminary clinical studies, dex-

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medetomidine has been shown to decrease thiopental anesthetic requirements by up to 50% in patients undergoing cervical dilatation and curettage.<sup>4,5</sup> 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 alpramethyl-dopa were excluded from the study. The sample size was based on a statistical power analysis ( $\beta = 0.2$  and  $\alpha = 0.05$ ) using data from a separate pilot study,<sup>6</sup> e.g., to find a

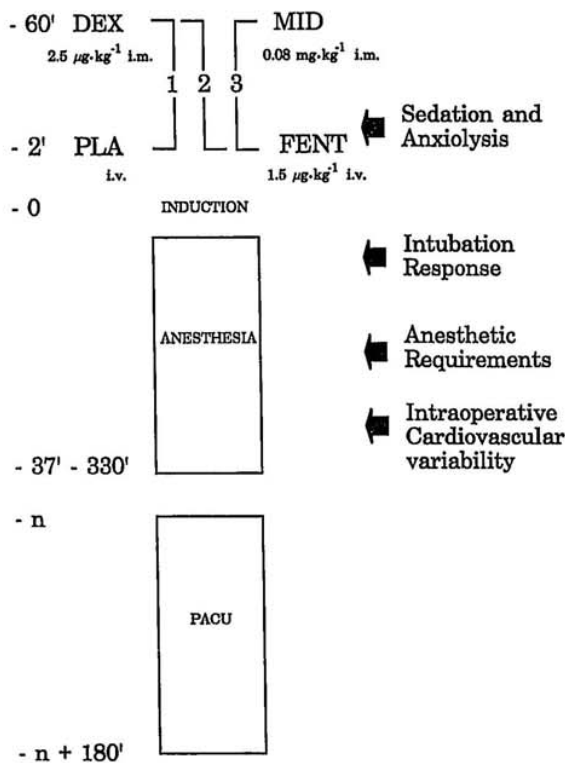


Fig. 1. Design and protocol-specified primary endpoints (response variables) of the study. 1 = DEXPLA; 2 = DEXFENT; 3 = MIDFENT. Differences in perioperative cardiovascular and blood oxygen saturation changes, numbers of intraoperative interventions, intra- and postoperative drug requirements, blood 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 Farnos, 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-

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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<sub>5</sub> 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<sub>2</sub>.

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<sub>2</sub>O/O<sub>2</sub>, 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- $\mu$ g/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  $\alpha$ - and  $\beta$ <sub>1</sub>-agonist properties,<sup>7</sup> 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 · kg<sup>-1</sup> · h<sup>-1</sup>. 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 (Plasmasfusin, 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<sub>2</sub> 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

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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  $\beta$ -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.

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