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ORIGINAL ARTICLE

Comparison of the effects of fentanyl, remifentanil, and dexmedetomidine on neuromuscular blockade

Ayse Ozcan · Namik Ozcan · Handan Gulec · Fatma Yalcin · Hulya Basar

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Abstract
Purpose The aim of our study was to compare the effects of fentanyl, remifentanil, and dexmedetomidine on neuromuscular blockade under sevoflurane anesthesia.
Methods Eighty-four patients were randomized to fentanyl, remifentanil, and dexmedetomidine groups. In the fentanyl group, fentanyl 1.5 μg/kg was given before induction of anesthesia, and additional 50-μg boluses were administered. In the remifentanil group, the initial dose of remifentanil 1 μg/kg was infused in 10 min before induction and 0.1 μg/kg/min infusion was continued during anesthesia. In the dexmedetomidine group, the initial dose of dexmedetomidine 1 μg/kg was infused in 10 min before induction and 1 μg/kg/h infusion was continued during anesthesia. Heart rate, blood pressure, SpO_2, $EtCO_2$, and TOF (train-of-four) values of all patients were monitored during anesthesia. Times to reach TOF 0 and TOF 25% and intubation quality were recorded.
Results T_0 times and quality of intubation were found to be similar among the groups. T_{25} time was found to be significantly longer in the dexmedetomidine group than in the fentanyl and remifentanil groups.
Conclusion Dexmedetomidine infusion increased the duration of neuromuscular blockade with vecuronium during general anesthesia. In addition to analgesic and sedative effects, dexmedetomidine may enhance the duration of neuromuscular blockade and may be used as an adjuvant anesthetic during general anesthesia.

Keywords Alpha-2 agonists · Dexmedetomidine · Opioids · Remifentanil · Neuromuscular blockade · Anesthesia

Introduction

A variety of drugs interacting with each other are used in general anesthesia practice. Concurrent administration of these drugs could affect the actions of each. Opioids and alpha-2 agonists are commonly used as anesthetic adjuvants. The effects of these coadministered drugs on neuromuscular blockade have not been extensively studied. There are only a few conflicting studies concerning the effect of dexmedetomidine on neuromuscular blockade. In volunteers, dexmedetomidine enhanced rocuronium-induced muscle relaxation [1], but it did not significantly alter vecuronium-induced muscle relaxation in rats in vivo [2]. There are no reports showing the effect of fentanyl and remifentanil on neuromuscular blockade.

The aim of this study was to determine and compare the effects of fentanyl, remifentanil, and dexmedetomidine on onset time and duration of neuromuscular blockade of vecuronium under sevoflurane anesthesia.

A. Ozcan · N. Ozcan · H. Basar
Department of Anesthesiology and Reanimation, Ankara Training and Research Hospital, Ankara, Turkey

A. Ozcan (✉)
1506 Cadde Ucler Safir Evleri 24/5 Cigdem, 06520 Ankara, Turkey
e-mail: ayseongun@gmail.com

H. Gulec
Department of Anesthesiology and Reanimation, Ankara Kecioren Training and Research Hospital, Ankara, Turkey

F. Yalcin
Department of Anesthesiology and Reanimation, Nallihan Hospital, Ankara, Turkey

Materials and methods

After approval of the Ethics Committee and written informed consent of the patients, 84 ASA I–II patients, 18–70 years old, undergoing elective surgery were enrolled to the study. Patients who had a history of cardiac, pulmonary, renal, hepatic, or neuromuscular disease, with a history of alcohol or drug abuse, or with anemia, serum electrolyte abnormalities, or marked obesity exceeding standard body weight by 20% or more, were excluded. None of the patients had a history of medication known to interact with neuromuscular blocking agents.

At arrival to the operating room, a hand vein was cannulated with a 20-G catheter, and electrocardiogram (ECG), noninvasive arterial blood pressure (NIBP), and arterial oxygen saturation (SpO_2) were monitored and values measured.

After baseline measurements, each patient was randomly (using a computer program) assigned to one of the fentanyl, remifentanil, and dexmedetomidine groups. In the fentanyl group (group F, $n = 30$), fentanyl was infused as a 1.5 μg/kg bolus before induction of general anesthesia and additional 50-μg boluses were administered according to hemodynamic changes (20% increase in systolic blood pressure or heart rate compared to baseline) during surgery. In the remifentanil group (group R, $n = 25$), initial remifentanil dose was 1 μg/kg, infused in 10 min before induction of general anesthesia, and 0.1 μg/kg/min infusion was continued until the end of surgery. In the dexmedetomidine group (group D, $n = 29$), the initial dexmedetomidine dose was 1 μg/kg, infused in 10 min before induction of general anesthesia, and 1 μg/kg/h infusion was continued until the end of surgery. After administration of initial doses of fentanyl, remifentanil, and dexmedetomidine was complete, anesthesia was induced with 5 mg/kg thiopental sodium and the trachea was intubated following administration of vecuronium bromide 0.1 mg/kg, when the train-of-four (TOF) value reached 0 (disappearance of all four twitches). Anesthesia was maintained with 2% sevoflurane and 50% nitrous oxide. Ventilation was adjusted to maintain end-tidal CO_2 between 35 and 40 mmHg. Heart rate, blood pressure, SpO_2, and end-tidal CO_2 ($EtCO_2$) values of all patients were monitored during anesthesia. Intraoperative infusion doses of both remifentanil and dexmedetomidine were adjusted according to hemodynamic changes (20% increase or decrease in systolic blood pressure or heart rate compared to baseline), whereas sevoflurane concentration stayed constant during anesthesia.

Neuromuscular block was monitored by TOF acceleromyography (TOF Watch S; Organon Ireland, Dublin, Ireland) applied to the ulnar nerve. The area above the ulnar nerve was cleaned to provide adequate contact of the electrodes. After thiopental administration, the nerve stimulator was switched on, and the automatic calibration procedure was started with 50 mA current, which was the default value of the device, to apply a supramaximal stimulus. After this, the stimuli was changed to TOF pattern, with 0.2 ms at 2 Hz delivered every 12 s via surface electrodes.

Times to reach TOF value 0 (T_0) and TOF value 25% (T_{25}) were recorded. T_0 was the time between injection of vecuronium and TOF value reaching 0 (disappearance of all four twitches) and was taken as the onset time. T_{25} was the time between T_0 and return of the TOF value to 25% (ratio of fourth twitch to first twitch) and was taken as clinical duration of neuromuscular blockade.

Intubating score was evaluated according to the consensus conference on good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents [3]. Five factors were considered for assessment: ease of laryngoscopy (jaw relaxation, resistance to laryngoscope), position and movement of vocal cords, airway reaction, and movement of limbs. The intubating score was considered excellent if all variables were excellent, good if all variables were excellent or good, and poor if any variable was poor.

Side effects such as bradycardia (<50 bpm), hypotension [mean arterial pressure (MAP) <60 mmHg], allergic reactions, and respiratory depression (respiratory rate <8/min) were also recorded. In case of bradycardia, atropine 0.5 mg i.v. would be administered; if bradycardia persisted the same dose would be repeated. Ephedrine 5 mg i.v. was planned to be administered for treatment of hypotension, repeated in the same dose if required.

Statistical analysis was performed by using the Medcalc software programme (Medcalc Software, Mariakerke, Belgium), version 11.3.3.0. We performed a pilot study of 10 patients with fentanyl for power analysis. We found T_{25} times were 51.3 ± 10.5 min. Power analysis revealed a sample size of 24 patients for each group to detect a change of 20% in T_{25} times with type 1 error ($\alpha = 0.01$) and type 2 error ($\beta = 0.01$). The Kolmogorov–Smirnov test was used to analyze the normal distribution of all variables. Intergroup comparisons were made with analysis of variance (ANOVA) followed by the Student–Newman–Keuls test for pairwise comparison of subgroups or Kruskal–Wallis variance test. The Chi-square test was used for comparison of categorical data. Data are presented as the mean ± SD. $P < 0.05$ was considered statistically significant.

Results

Characteristics of the patients [age, gender, height, weight, body mass index (BMI)] and duration of surgery are shown in Table 1.

Table 1 Patient characteristics and duration of surgery

	Group F	Group R	Group D	*P* value
Age (years)	39 ± 16	41 ± 15	36 ± 14	0.554
Gender (M/F)	10/20	7/18	11/18	0.74 ($\chi^2 = 0.60$)
Height (cm)	164 ± 8	165 ± 8	166 ± 8	0.775
Weight (kg)	73.4 ± 20	72.2 ± 11.2	69.4 ± 15.7	0.572
Body mass index (BMI)	27.2 ± 7.0	26.6 ± 3.9	25.3 ± 5.7	0.355
Duration of surgery (min)	81 ± 12	90 ± 22	92 ± 23	0.166

F fentanyl, *R* remifentanil, *D* dexmedetomidine

Values are mean ± SD and numbers (proportion)

Table 2 T_0, T_{25} times and intubation quality of groups

	Group F	Group R	Group D	*P* value
T_0 (s)	174 ± 67	173 ± 59	149 ± 35	0.251
T_{25} (min)	54 ± 13	57 ± 10	68 ± 19*	0.001
Intubation quality (excellent/good/poor)	19/10/1	15/9/1	22/5/2	0.55 ($\chi^2 = 3.045$)

Values are mean ± SD and numbers (proportion)

* $P < 0.05$ versus remifentanil and fentanyl groups

Infusion of remifentanil or dexmedetomidine alone before the induction of general anesthesia did not affect MAP, heart rate, or SpO_2 in any patient.

The infusion rates required were between 0.05 and 0.15 μg/kg/min and from 0.5 to 1 μg/kg/h for remifentanil and dexmedetomidine, respectively.

There were no differences in T_0 among the three groups ($P = 0.251$) (Table 2).

T_{25} was found to be significantly longer in dexmedetomidine group than in fentanyl and remifentanil groups ($P = 0.001$) (Table 2).

The quality of intubation was similar between groups ($P = 0.55$). The rate of excellent intubating scores was 19, 15, and 22 in fentanyl, remifentanil, and dexmedetomidine groups, respectively. The rate of clinically acceptable scores (excellent or good) was 29 in the fentanyl group, 24 in the remifentanil group, and 27 in the dexmedetomidine group (Table 2).

Hypotension was observed in one and in two patients of the fentanyl and remifentanil groups, respectively. Ephedrine 5–10 mg i.v. was used for two patients in the remifentanil group. Also, bradycardia was seen in the same two patients of the remifentanil group, but atropine was not needed.

Discussion

The result of the present study demonstrated that dexmedetomidine infusion increased the duration of neuromuscular blockade compared to fentanyl and remifentanil during general anesthesia.

Inhalational anesthetics, local anesthetics, and certain other drugs are known to increase the duration of neuromuscular blocking agents [4]. However, there are no reports of the effect of fentanyl or remifentanil on neuromuscular blockade. Although we observed no difference between the effects of fentanyl and remifentanil on neuromuscular blockade, the absence of a control group for these two groups might hide the possible effects of fentanyl or remifentanil on neuromuscular blockade.

Results concerning the effects of dexmedetomidine on neuromuscular blockade are conflicting in the literature. Some articles report enhancement or no significant effect of alpha-2 agonists on neuromuscular blockade [5, 6]. In our study, dexmedetomidine shortened the T_0 time by approximately 25 s. This result was not statistically significant but could be considerable clinically. The onset time of a neuromuscular blocker is primarily determined by cardiac output and muscle blood flow [7]. Although dexmedetomidine decreases cardiac output in a dose-dependent manner [8, 9], onset time of the muscle relaxant was found to be shorter in the dexmedetomidine group. This result needs further investigation with larger groups.

T_{25} time was significantly longer in the dexmedetomidine group than in fentanyl and remifentanil groups. We tried to explain this result with a few possible mechanisms. In one study, Talke et al. found that after administration of dexmedetomidine, plasma rocuronium concentrations increased and T_1 (first twitch in the TOF sequence) decreased. They also observed a decrease in finger blood volume and an increase in systemic blood pressure, which was thought to be associated with dexmedetomidine-induced peripheral vasoconstriction [1, 10]. The pharmacokinetic mechanisms, influenced by dexmedetomidine, may explain the increase in the plasma rocuronium concentration [1]. Dexmedetomidine also decreases both renal and hepatic blood flow [11]. Vecuronium bromide is eliminated extensively by the liver [6]. The pharmacokinetic changes caused by dexmedetomidine may retard the elimination of vecuronium and delay the recovery of neuromuscular block, which may be a possible mechanism valid in our study.

Epinephrine and norepinephrine were reported to antagonize the neuromuscular block of tubocurarine and

enhance acetylcholine release from prejunctional sites in skeletal muscles in experimental studies. Clonidine, another alpha-2 agonist, inhibits norepinephrine release from sympathetic nerve terminals and decreases the plasma concentration of norepinephrine. Also, it has been reported that stimulation of presynaptic alpha-2 adrenoceptors inhibits the release of acetylcholine in the central nervous system. Therefore, clonidine may potentiate the neuromuscular blocking effects of a nondepolarizing muscle relaxant [6]. Dexmedetomidine is more potent and 27 times more selective for alpha-2 receptors than clonidine [12, 13]. Also dexmedetomidine may show same effects on neuromuscular blockade and could have prolonged the T_{25} time in our study.

Narimatsu et al. [14] showed that high concentrations of clonidine and dexmedetomidine enhance the neuromuscular blocking action of rocuronium at the rat diaphragm. They concluded this was a result of competitive or noncompetitive blockade of postjunctional, muscle-type nicotinic acetylcholine receptors, a non-alpha-2 adrenergic mechanism by dexmedetomidine [14–16].

Our study has some limitations. First, we studied the effect of fentanyl, remifentanil, and dexmedetomidine on the neuromuscular blocking effect of vecuronium, so we could only say that dexmedetomidine prolongs the duration of a vecuronium-induced neuromuscular blockade compared to fentanyl and remifentanil. Although we did not observe any difference between the effects of fentanyl and remifentanil, the lack of a control group limited our results concerning these agents. Second, we were not able to measure the plasma levels of vecuronium to show possible changes in the pharmacokinetics of vecuronium. We also could not measure the levels of catecholamines to show that decrease in catecholamine release lengthened the duration of neuromuscular block induced by vecuronium.

As a summary, T_{25} time was significantly longer in the dexmedetomidine group than in the fentanyl and remifentanil groups. This result may be caused by changes in the pharmacokinetics of vecuronium caused by dexmedetomidine, blockade of muscle-type nicotinic acetylcholine receptors by dexmedetomidine, or changes in plasma catecholamine levels from the central effects of dexmedetomidine.

The present study is one of the rare studies assessing the effects of fentanyl, remifentanil, and dexmedetomidine on neuromuscular blockade in vivo. It was also performed in patients under general anesthesia. We concluded that, in addition to analgesic and sedative effects, dexmedetomidine may enhance the duration of neuromuscular blockade. Further studies will be able to show effects and the possible mechanism of action of dexmedetomidine on neuromuscular blockade of muscle-relaxing drugs.

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