Article Title

Low-dose droperidol suppresses transcranial electrical motor-evoked potential amplitude: a retrospective study

Author Information

Hiroyuki Deguchi[1], Kenta Furutani[1*], Yusuke Mitsuma[1], Yoshinori Kamiya[1], Hiroshi Baba[1]

[1]Department of Anesthesiology, Niigata University Graduate School of Medical and Dental Sciences

Address: 1-757 Asahimachi-Dori, Chuo-ku, Niigata 951-8510, Japan

[*]**Corresponding author**

Kenta Furutani

Department of Anesthesiology, Niigata University Graduate School of Medical and Dental Sciences

Address: 1-757 Asahimachi-Dori, Chuo-ku, Niigata 951-8510, Japan

E-mail: kenta-f@med.niigata-u.ac.jp

Phone: +81-25-227-2328

FAX: +81-25-227-0790

Acknowledgments

We would like to thank Editage (www.editage.jp) for English language editing and Satista Inc. for statistical analysis.

Previous presentations

Japanese Society of Anesthesiologists Annual Meeting; May 17, 2018, Yokohama, Japan

Abstract

Purpose

Low-dose droperidol has been widely used as an antiemetic during and after surgery. Although high-dose droperidol affects motor-evoked potential, the effects of low-dose droperidol on motor-evoked potential amplitude are unclear. The aim of this study was to investigate whether low-dose droperidol affects motor-evoked potential amplitude.

Methods

We retrospectively reviewed the data of patients who underwent spine surgery under general anesthesia with motor-evoked potential monitoring from February 2016 to February 2017. The outcome was the motor-evoked potential amplitude of the bilateral abductor pollicis brevis muscle, tibialis anterior muscle, and abductor hallucis muscle within 1 and 1–2 hours after droperidol administration, compared with the baseline motor-evoked potential value.

Results

Thirty-four patients were analyzed. The median dose of droperidol was 21 μg/kg.

The motor-evoked potential amplitudes of all muscles were significantly reduced after droperidol administration and recovered to baseline values within 2 hours. The reduction of all motor-evoked potential amplitudes after droperidol administration was 37–45% of baseline values. There were no significant differences in other drugs administered. There were no serious adverse effects of droperidol administration.

Conclusion

Motor-evoked potential amplitude was suppressed by low-dose droperidol. During intraoperative motor-evoked potential monitoring in spine surgery, anesthesiologists should pay careful attention to the timing of administration of droperidol, even at low doses. Based on the results of this study, we are conducting a randomized controlled trial.

Keywords: motor-evoked potential, droperidol, intraoperative monitoring, general anesthesia

Introduction

Low-dose droperidol (15–20 μg/kg or 0.625–2.5 mg) has been used as an antiemetic, and significantly reduces the incidence of postoperative nausea and vomiting (PONV). In 2001, the US Food and Drug Administration warned consumers of the risk of QT segment prolongation due to droperidol use; however, low-dose droperidol remains widely used without severe complications, such as cardiac arrhythmias, in some countries because the risks of droperidol use are dose-dependent [1-3].

Motor-evoked potential (MEP) measurement is a useful intraoperative monitoring technique to detect damage to the pyramidal tract during spine surgery [4-7]. However, various factors affect MEP amplitude. For example, anesthetic drugs such as volatile anesthetics and propofol dose dependently decrease MEP amplitude [8]. High-dose droperidol (70 μg/kg) was also reported to decrease transcranial magnetic MEP (TCM-MEP) amplitude [9]. However, the effect of low-dose droperidol on MEP amplitude is largely unknown, with only a single case series that reported that low-dose droperidol (1–1.25 mg) decreased transcranial electric MEP (TCE-MEP) amplitude [10].

We aimed to clarify the effects of antiemetic low-dose droperidol on TCE-MEP and to improve the quality of intraoperative neurological monitoring. Hence, we performed a retrospective study to investigate whether low-dose droperidol suppresses TCE-MEP amplitude under general anesthesia.

Materials and Methods

Patients

This study was approved by the Ethics Committee of Niigata University Medical and Dental Hospital, Niigata, Japan (Approval No. 2017-0246). The Ethics Committee waived the requirement for written informed consent due to the retrospective nature of this study; however, patients received opt-out notices on the hospital's web site and information flyers were posted in the hospital. We retrospectively reviewed the data of patients who underwent spine surgery under general anesthesia with TCE-MEP monitoring from February 2016 to February 2017 at Niigata University Medical and Dental Hospital, Niigata, Japan. The inclusion criteria were patients whose TCE-MEP amplitudes were measured at three time points (T0: before droperidol administration as a baseline value, T1: within 1 hour after droperidol administration, T2: 1–2 hours after droperidol administration). The exclusion criteria included patients who did not undergo TCE-MEP amplitude measurement at the three different time points (T0, T1, and T2), patients who

had changed their posture (e.g., from lateral decubitus position to prone position) within 2 hours of droperidol administration, and patients from whom TCE-MEP waveforms could not be obtained in all muscles due to pre-existing neurological symptoms or technical problems.

General Anesthesia

General anesthesia was maintained with propofol, remifentanil, and fentanyl in all patients. Propofol was administered using a target-controlled infusion pump (TE-371, Terumo, Tokyo, Japan). The infusion rate of propofol was adjusted to maintain bispectral index (BIS) values in the range of 40–60 and suppression ratios of 0. Remifentanil was administered at 0.1–0.5 μg/kg/min. Bolus doses of fentanyl (50–200 μg) were administered repeatedly to maintain the simulated effect site concentration above 1 ng/ml for intra- and postoperative analgesia. Rocuronium (0.6–0.9 mg/kg) was administered to facilitate tracheal intubation, and the neuromuscular blocking effect of rocuronium was reversed by sugammadex (2–4 mg/kg) before TCE-MEP recording to maximize the TCE-MEP

amplitude. In all cases electrocardiography results and invasive blood pressure, pulse oximetry, partial pressure of end-tidal carbon dioxide, and body temperature values were monitored. If systolic blood pressure was less than 90 mmHg, ephedrine or phenylephrine was administered. External heating devices were used to maintain body temperatures. Intravenous patient-controlled analgesia (IV-PCA) (fentanyl combined with ketamine and droperidol) was used postoperatively.

MEP recordings

We used an intraoperative neurophysiological monitoring system (Neuromaster MEE-1232, Nihon Kohden, Tokyo, Japan). An anesthesiologist who was an expert in neurophysiological monitoring recorded and evaluated MEP. TCE-MEP was elicited by a train of five pulses with inter-stimulus intervals of 2 ms (low cut filter 10 Hz and high cut filter 3 kHz), using a constant-voltage stimulator (SEN-4100, Nihon Kohden, Tokyo, Japan). Stimulus intensity was initiated at 300 V and increased by 50 V increments until the intensity reached supramaximal stimulation. A pair of corkscrew electrodes

(SN-100-1500AD, Unique medical, Tokyo, Japan) were fixed at C3 (cathode) and C4 (anode) (international 10-20 system). Adhesive gel Ag-AgCl electrodes (NM314YL, Nihon Kohden, Tokyo, Japan) were attached on the skin and used for TCE-MEP recording. TCE-MEP amplitude was measured as peak to peak amplitude.

Outcomes

We analyzed the TCE-MEP amplitudes of the bilateral abductor pollicis brevis muscle (APB), tibialis anterior muscle (TA), and abductor hallucis muscle (AH) at T0, T1, and T2. The baseline value of MEP was defined as the MEP recorded before administration of droperidol (T0). In addition, we collected data on pulse rate, mean blood pressure, partial pressure of end-tidal carbon dioxide, pulse oximetry, body temperature, dose and simulated effect site concentration of remifentanil and fentanyl, and the BIS value from the anesthesia records. The patients' demographic data including age, sex, height, and weight were also recorded.

The effect site concentration of remifentanil was calculated from the

137 administration rate using the pharmacokinetic models reported by Minto and Kunisawa
138 [11-13]. In addition, the effect site concentration of fentanyl was calculated using the
139 Shafer model [14, 15].
140
141 **Statistical analysis**
142 Patients' demographic data and droperidol dose were expressed as median and
143 range [minimum-maximum]. Other continuous variables with non-parametric distribution
144 were expressed as median and interquartile range [25%, 75%]. Bilateral TCE-MEP
145 amplitudes obtained from the same patient were analyzed together. Statistical analyses of
146 bilateral TCE-MEP amplitudes (APB, TA, AH), dosages of other drugs (propofol,
147 remifentanil, fentanyl), and vital signs (pulse rate, mean blood pressure, partial pressure of
148 end-tidal carbon dioxide, pulse oximetry, body temperature, BIS value) that were obtained
149 at the three different time points (T0, T1, and T2) were performed using the Friedman test.
150 The Wilcoxon signed rank test adjusted by Bonferroni correction was used for post hoc
151 analysis when significance was determined by the Friedman test. During analysis,

completion of missing values was not performed. All statistical tests were two-sided, and statistical significance was defined by a p-value < 0.05. Statistical analyses were performed using R version 3.2.4.

156 **Results**

157 Fifty patients underwent spine surgery with TCE-MEP monitoring during the
158 period studied. Sixteen patients were excluded for the following reasons: TCE-MEP was
159 not measured at T1 and T2 (n=11 patients); TCE-MEP could not be obtained in all muscles
160 due to pre-existing neurological symptoms or technical problems (n=4 patients); posture
161 was changed within 1 hour after droperidol administration (n=1 patient). Although
162 TCE-MEP amplitude could not be obtained at the bilateral APB in one patient, the other
163 two sites (TA, AH) in that patient were included in the analysis. Therefore, 34 patients' data
164 (APB: 66 sites, TA: 68 sites, AH: 68 sites) were analyzed (Fig 1). The demographic data are
165 presented in Table 1. The median dose of droperidol was 21 μg/kg. Heart rate was increased
166 at T2, compared to T1. Body temperature increased over time. Propofol was significantly
167 different by Friedman test, but not by post hoc analysis. There were no significant
168 differences in other vital signs or other drugs administered (Table 2). The TCE-MEP
169 amplitudes of all muscles were significantly reduced at T1 and recovered to baseline values
170 at T2 (Table 3; Fig 2). The median reductions of TCE-MEP recorded from each muscle

171 after droperidol administration were 37%–45% of baseline value. There were no adverse
172 events such as torsades de pointes, severe hypotension, extrapyramidal symptoms, or
173 neurological symptoms in the perioperative period.
174

Discussion

This study showed that low-dose droperidol (approximately 20 μg/kg) reduced TCE-MEP amplitude and that the median reductions of TCE-MEP were 37%–45% of baseline values.

Previous studies have revealed that high-dose droperidol, 70 μg/kg and 300 μg/kg, suppresses TCM-MEP amplitude in humans [9] and monkeys [16], respectively. However, there have been no clinical trials to demonstrate whether low-dose droperidol, which is used as an antiemetic, affects TCE-MEP amplitude. A recent case report regarding a 58-year-old woman suggested that low-dose droperidol (1.25 mg) could reduce the TCE-MEP amplitude [10]. Our retrospective analysis in a more comprehensive patient cohort supports this finding.

Notably, the reduction rate of TCE-MEP amplitude in this study reached the approximate clinical alarm point. Although clinical alarm points of TCE-MEP amplitude to avoid neurological damage in the spine surgery are not clearly defined, most reports conclude that a 50%–80% decrease of TCE-MEP amplitude is clinically relevant [5-7, 17].

190 Hence, the attenuation of TCE-MEP amplitude in response to low-dose droperidol could
191 cause false-positives. Because there have been no previous reports to demonstrate the
192 influence of low-dose droperidol on TCE-MEP amplitude, technologists/monitoring
193 physicians cannot diagnose that the reduction of TCE-MEP amplitude is the effect of
194 droperidol, which would lead to false-positive results. Our research results suggest that we
195 should obtain both new baselines after administration of droperidol and sufficiently
196 frequent TCE-MEP measurements repeatedly to account for the time-varying effects of the
197 drug post-administration without causing false-positives. In addition, during intraoperative
198 TCE-MEP monitoring in spine surgery, anesthesiologists should avoid droperidol
199 administration during a crucial surgical manipulation, even when using a low dose.
200 Therefore, it is crucial to clarify the effect of low-dose droperidol on TCE-MEP amplitude
201 in a randomized controlled trial.

202 IV-PCA using opioids is an essential analgesic method for postoperative pain
203 management but represents a risk factor of PONV [18, 19]. The median dose of droperidol
204 in this study was 21 μg/kg. According to previous reports, doses of droperidol similar to

that used in this study (1–1.25 mg or 15–20 μg/kg) prevent nausea and vomiting in the early postoperative period [20]. Therefore, our dosage regimen of droperidol was thought to be effective for the prevention of PONV. Therefore, the results of our study could improve both the quality of life postoperatively [21], as well as quality of postoperative analgesia and intraoperative neurophysiological monitoring, together leading to safer surgery.

The mechanisms underlying the effects of low-dose droperidol are unknown. The antiemetic effect of droperidol is thought to result from inhibition of the D2 receptor [22-24]. Droperidol has no specific pharmacological targets, and can act as a γ-aminobutyric acid type A receptor antagonist/agonist, a nicotinic acetylcholine receptor antagonist, and a sodium channel blocker [25, 26]. Droperidol is reported to suppress spontaneous electrical activity in neurons [27]. Therefore, it is reasonable to hypothesize that droperidol attenuates the amplitude of TCE-MEP, which are elicited by the sum of neuronal excitations in the motor system by inhibiting excitatory neurotransmissions.

Limitations

This study had some limitations. First, this was a single-center, retrospective

220 study with a small number of patients. Patients' background, doses of droperidol, and
221 timing of TCE-MEP recording, as well as the other anesthesia regimens were not uniform.
222 Especially, there was large variation in age and diseases among the surgically treated
223 patients. Therefore, we could not exclude the possibility of the influence of the surgical
224 procedure in increasing or decreasing the TCE-MEP amplitude on our outcome measures.
225 However, because the reduction of TCE-MEP amplitude after the administration of
226 droperidol was reversible, we do not think that the surgical procedure affected our results.
227 Second, we could not confirm the train of four ratio from the anesthetic records. However,
228 rocuronium bromide was administered only at the induction of general anesthesia. Besides,
229 we administered sugammadex to reverse the effect of rocuronium before the TCE-MEP
230 recording. Even if the effect of rocuronium remained, it would be too small to reduce the
231 TCE-MEP amplitude. Therefore, we do not think that the residual effect of rocuronium
232 affected the results of the study. Third, we could not exclude the influence of trial-to-trial
233 variability on TCE-MEP amplitude because the present study was a retrospective study
234 without a placebo group. However, if the trial-to-trial variability affected the results of this

study, the variability would affect not only the MEP amplitude at T1 but also those at T0 and T2. Besides, the MEP amplitudes at T2 were recovered from those at T1 with a statistically significant difference. Therefore, it is reasonable to state that the reduction of TCE-MEP amplitude at T1 was due to droperidol administration.

Conclusions

TCE-MEP amplitude was suppressed by low-dose droperidol administration for the prevention of PONV. During intraoperative TCE-MEP monitoring in spine surgery, anesthesiologists should pay careful attention to the timing of droperidol administration, even if using a low dose. We are conducting a randomized controlled trial to further validate these findings.

Author contributions

Conceptualization and Methodology: Hiroyuki Deguchi, Kenta Furutani; Formal analysis, data curation, investigation: Hiroyuki Deguchi, Yusuke Mitsuma; Writing - original draft preparation: Hiroyuki Deguchi; Writing - review and editing: Kenta Furutani, Yoshinori

Kamiya, Hiroshi Baba; Supervision: Kenta Furutani, Yoshinori Kamiya, Hiroshi Baba.

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Figure captions

Fig. 1 Participant Flow Diagram.

TCE-MEP, transcranial electric motor-evoked potential

Fig. 2 Box-Plot Diagrams of Transcranial Electric Motor-Evoked Potential Amplitudes of Each Muscle.

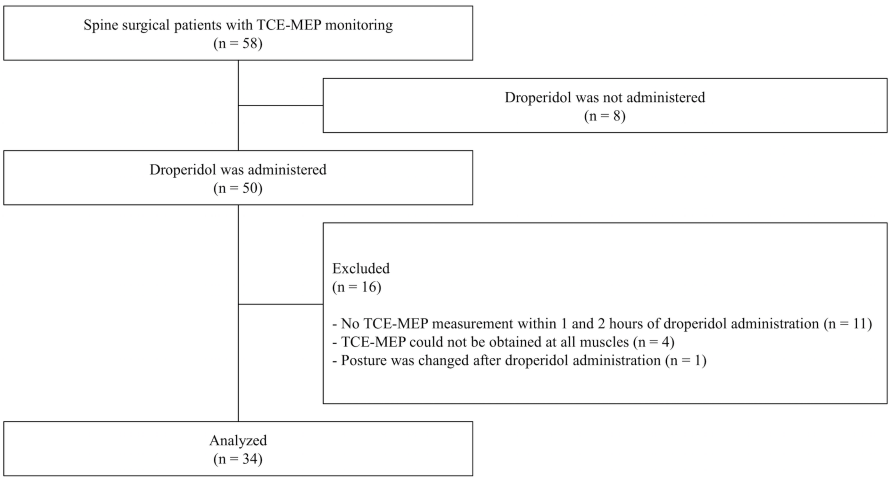
Transcranial electric motor-evoked potential amplitudes recorded from each muscle after droperidol administration were significantly reduced and recovered to baseline values within 2 hours (T0 and T2 were not significantly different).

T0: before droperidol administration.

T1: within 1 hour after droperidol administration.

T2: 1–2 hours after droperidol administration.

*: $P < 0.0001$. P-values are according to Wilcoxon signed-rank test, with Bonferroni adjustment. APB, abductor pollicis muscle; TA, tibialis anterior muscle; AH, abductor hallucis muscle


Spine surgical patients with TCE-MEP monitoring
(n = 58)
Droperidol was not administered
(n = 8)
Droperidol was administered
(n = 50)
Excluded
(n = 16)
- No TCE-MEP measurement within 1 and 2 hours of droperidol administration (n = 11)
- TCE-MEP could not be obtained at all muscles (n = 4)
- Posture was changed after droperidol administration (n = 1)
Analyzed
(n = 34)

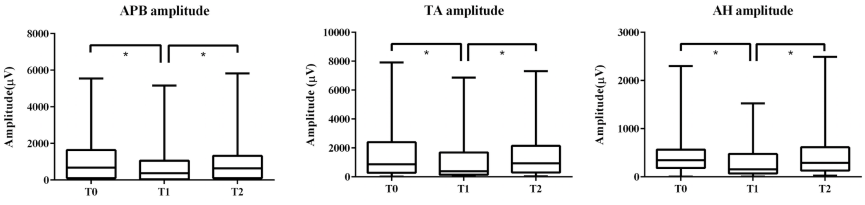

APB amplitude
Amplitude(μV)
8000
6000
4000
2000
0
T0
T1
T2
*
*
TA amplitude
Amplitude (μV)
10000
8000
6000
4000
2000
0
T0
T1
T2
*
*
AH amplitude
Amplitude(μV)
3000
2000
1000
0
T0
T1
T2
*
*

Table 1. Characteristics of patients and droperidol dose.

Characteristics	n = 34	
Gender male	8	(23.5 %)
Age (years)	22	[12-80]
Height (cm)	154.6	[129.6-182.0]
Weight (kg)	51.2	[30.0-74.1]
Disease		
Scoliosis	20	(58.8 %)
Kyphosis	10	(29.4 %)
Spinal tumor	4	(11.8 %)
Surgical procedure		
Posterior spine fusion	25	(73.5 %)
Posterior spine fusion + Anterior spine fusion	7	(20.6 %)
Tumor resection	2	(5.9 %)
Droperidol dose (mcg/kg)	21	[16-28]

Data are expressed as median [range] or number (%).

Table 2. Anesthetics and demographic data for 3 groups of droperidol administration.

	n	T0		T1		T2		P-value‡
Propofol TCI (μg/ml)	34	2.9	[2.5, 3.0]	2.8	[2.6, 3.0]	2.8	[2.6, 3.0]	0.004
Remifentanil (μg/kg/min)	34	0.2	[0.2, 0.2]	0.2	[0.2, 0.2]	0.2	[0.2, 0.2]	0.59
Remifentanil (ng/ml)	34	3.38	[2.78, 4.37]	3.56	[3.09, 4.75]	3.52	[3.09, 4.75]	0.59
Fentanyl (ng/ml)	34	2.11	[0.98, 3.21]	2.06	[1.65, 2.96]	2.03	[1.58, 2.41]	0.85
Heart rate (bpm)	34	61	[54, 75]	65	[59, 73]	69†	[60, 78]	0.006
Mean blood pressure (mmHg)	34	66	[63, 74]	66	[59, 73]	66	[61, 69]	0.34
$ETCO_2$ (mmHg)	34	34	[32, 36]	34	[33, 36]	34	[33, 36]	0.75
SpO2 (%)	34	100	[100, 100]	100	[100, 100]	100	[100, 100]	0.18
Body temperature (ºC)	34	36.3	[35.9, 36.6]	36.4*	[35.9, 36.6]	36.5†	[36.1, 36.8]	0.0005
Bispectral index	34	50	[42, 57]	51	[45, 55]	53	[45, 59]	0.21

Data are expressed as median and interquartile range [25%, 75%].

T0: before droperidol administration.

T1: within 1 hour after droperidol administration.

T2: 1-2 hours after droperidol administration.

TCI, Target-controlled infusion; $ETCO_2$, partial pressure of end-tidal carbon dioxide; SpO2, percutaneous oxygen saturation.

*$P < 0.05$ (T1 vs T2). P values are according to Wilcoxon signed-rank test, with Bonferroni adjustment.

†$P < 0.05$ (T0 vs T2). P values are according to Wilcoxon signed-rank test, with Bonferroni adjustment.

‡Friedman test.

Table 3. TCE-MEP amplitudes for each group.

	n	T0		T1		T2		P-value[§]
APB amplitude (μV)	66	682	[113, 1583]	378[*†]	[40, 1029]	645[‡]	[115, 1280]	< 0.0001
TA	68	872	[299, 2361]	385[*†]	[150, 1681]	937[‡]	[311, 2109]	< 0.0001
AH	68	343	[189, 553]	156[*†]	[70, 473]	291[‡]	[136, 609]	< 0.0001

Droperidol significantly decreased the TCE-MEP amplitudes recorded from bilateral APB, TA, and AH muscles.

Data are expressed as median and interquartile range [25%, 75%].

T0: before droperidol administration.

T1: within 1 hour after droperidol administration.

T2: 1-2 hours after droperidol administration.

TCE-MEP, transcranial electric motor-evoked potential; APB, abductor pollicis muscle; TA, Tibialis anterior muscle; AH, Abductor hallucis muscle.

[*]P < 0.0001 (T1 vs T0). P values are according to Wilcoxon signed-rank test, with Bonferroni adjustment.

[†]P < 0.0001 (T1 vs T2). P values are according to Wilcoxon signed-rank test, with Bonferroni adjustment.

[‡]P > 0.05 (T0 vs T2). P values are according to Wilcoxon signed-rank test, with Bonferroni adjustment.

[§]Friedman test.