

The effects of anesthetic agents on pupillary function during general anesthesia using the automated infrared quantitative pupillometer

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Abstract Pupil reactivity can be used to evaluate central nervous system function and can be measured using a quantitative pupillometer. However, whether anesthetic agents affect the accuracy of the technique remains unclear. We examined the effects of anesthetic agents on pupillary reactivity. Thirty-five patients scheduled for breast or thyroid surgery were enrolled in the study. Patients were divided into four groups based on the technique used to maintain anesthesia: a sevoflurane–remifentanyl (SEV/REM) group, a sevoflurane (SEV) group, a desflurane–remifentanyl (DES/REM) group, and a propofol–remifentanyl (PRO/REM) group. We measured maximum resting pupil size (MAX), reduction pupil size ratio (%CH), latency duration (LAT) and neurological pupil index (NPi). A marked reduction in MAX and %CH compared with baseline was observed in all groups, but LAT was unchanged during surgery. NPi reduced within the first hour of surgery in the SEV/REM, SEV, and DES/REM groups, but was not significantly different in the PRO/REM group. Compared with the PRO/REM group,

mean %CH and NPi in patients anesthetized with SEV/REM, SEV or DES/REM were markedly lower at 1 h after surgery had commenced. There was no correlation between NPi and bispectral index. Fentanyl given alone decreased pupil size and %CH in light reflex, but did not change the NPi. NPi was decreased by inhalational anesthesia not but intravenous anesthesia. The difference in pupil reactivity between inhalational anesthetic and propofol may indicate differences in the alteration of midbrain reflexes in patients under inhalational or intravenous anesthesia.

Keywords NPi · Pupil reactivity · Quantitative pupillometer

1 Introduction

It has been reported that pupillary reactivity measured using an infrared quantitative pupillometer is a useful tool of uncovering aspects of how the human pupil reacts to drug and noxious stimulation, or of detecting degree of brain damage [1–3]. The accuracy, objectivity and reproducibility of quantitative pupillary assessment are superior to those obtained manually at the bedside, even by experienced nurses and physicians [4]. The device automatically measures maximum (initial) resting pupil size (MAX), minimum pupil size after stimulation (MIN), reduction pupil size ratio (%CH, $[\text{MAX} - \text{MIN}] / \text{MAX}$ expressed as a percentage), latency duration (LAT, time between initiation of retinal light stimulation and onset of pupillary constriction), constriction velocity (CV, extent of constriction/duration of constriction), maximum constriction velocity (MCV), dilation velocity (DV, extent of pupil size recovery/duration of recovery) and neurological pupil index (NPi). The NPi is a proprietary parameter that is a

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unit less numerical value from 0 to 5 and allegedly indicates the quality of the light reflex: a value of 0 represents an absent light reflex, and a value of >3 is considered normal [5]. It has been reported that early normalization of the NPi after traumatic brain injury suggests that neurologic function may improve [6]. However, the pupillometer has not been widely used in the operating room so we cannot judge whether reduction of NPi is from the influence of anesthetic agents or from an intracranial abnormality. Although our preliminary data showed differences in pupillary reflex between inhalation and intravenous anesthetic, no study has investigated pupillary function, including the NPi, or has made comparisons between inhalation and intravenous anesthetic agents in surgery. Therefore, we were interested to observe how the various parameters of the pupillary light reflex are depressed by general anesthetics during various phases of the anesthetic. We hypothesized that inhalation anesthetics would depress the pupillary light reflex as measured by NPi but this depression would not be as pronounced when using a total intravenous anesthetic technique with propofol and remifentanyl.

2 Methods

2.1 Patients and study design

Conduct of the study was approved by the institutional clinical research ethics committee (Kyushu University, Fukuoka, Japan) and registered at UMIN-CTR (UMIN000017007). Thirty-five patients scheduled for breast or thyroid tumor resections surgery were enrolled. We excluded patients with cataract, glaucoma, an intraocular lens or insulin-dependent diabetes mellitus [1, 7]. Informed consent was obtained from all participants included in this study. The study was observational, non-randomized and not controlled. Pupillary measurements were recorded using a portable infrared quantitative pupillometer (NeuroOptics® NPiTM-100, Neurooptics Inc., Irvine, CA, USA). The light reflex was acquired by a flash of visible white light of 800 ms duration at the start of each 3.2-s scan [8]. We divided patients into one of four groups on the basis of anesthetic technique (see Table 1).

Pupillary reactivity was measured at baseline before induction of anesthesia (control), at the time of rocuronium administration (just after loss of consciousness: LOR), after endotracheal intubation (intubation), 1 h after the start of surgery (surgery) and just before return to the ward (recovery). In the DES/REM group, pupillary reactivity was measured 5 min after administration of fentanyl. For patients that received rocuronium, the train-of-four ratio was confirmed to be $>97\%$ 1 h after the start of surgery. In

the PRO/REM group we controlled BIS below 50 during surgery.

2.2 Statistical analysis

Power analysis ($\alpha = 0.05$, $\beta = 0.20$) indicated that a subject sample size of fewer than seven per group was needed to detect a significant difference in NPi 1 h after surgery had commenced between in the SEV/REM and PRO/REM group, using data collected in a preliminary study (SEV/REM: 4.4 ± 0.1 , $n = 5$ vs. PRO/REM: 3.7 ± 0.1 , $n = 5$; $p < 0.0001$). We enrolled 10 subjects per group to account for potential protocol failure or dropouts, apart from the SEV group, which comprised five subjects. All data are presented as the mean \pm standard deviation. The number of patients is denoted by n . Tukey's, Dunnett's or Kruskal–Wallis test multiple comparison post hoc tests were undertaken for one-way analysis of variance. The extent of dependence between BIS and NPi was determined using the multiple regression coefficients. p values <0.05 were considered statistically significant. Analyses except multiple regression coefficients were undertaken using Prism 6 software (GraphPad Software, CA USA). Multiple regression coefficients were undertaken using STAT version 11 (Stata corporation, Texas, USA).

3 Results

3.1 Patient characteristics and maintenance of anesthesia

Of the 35 patients, four were men (10.0 %). There were no significant differences in the mean weight, age or surgical time of the groups (not shown). The MAC of sevoflurane in the SEV/REM group was significantly lower than the SEV group (Table 1).

3.2 Pupillary reflexes

The relevant data are shown in Figs. 1, 2 and Tables 2, 3, 4, 5. Specifically it was observed that all anesthetics decreased the size of the pupil, with or without remifentanyl (Table 2) and decreased the extent of the light reflex as measured by %CH (Table 3). However, there was no change in the light reflex as measured by NPi in the PRO/REM group but inhalational anesthetics did depress this parameter (Fig. 1d). We also observed that the NPi did not change from control at LOC and intubation in the PRO/REM group (Table 4). Fentanyl decreased the size of the

Table 1 The basis of anesthetic technique in each group 1 h after surgery had commenced

	SEV/REM	SEV	DES/REM	PRO/REM
Premedication	–	–	–	–
Induction	Propofol	Propofol	Propofol	Propofol
Maintenance	SEV/REM	SEV	DES/REM	PRO/REM
Fentanyl	+	+	+	+
Rocuronium	+	–	+	+
Anesthetic depth monitor	MAC (0.56 ± 0.66)	MAC (0.66 ± 0.05) ^a	MAC (0.62 ± 0.04)	BIS (42 ± 6.9)
Airway	Intubation	LMA	Intubation	Intubation
Number	10	5	10	10

Data are presented as the mean ± standard deviation. One-way analysis of variance with Tukey’s multiple comparison test was used to compare each case with all others

MAC minimum alveolar concentration, LMA laryngeal mask, BIS bispectral index

^a **p* < 0.05 versus SEV/REM

Fig. 1 Comparison of maximum, reduction pupil size ratio, latency and neurological pupillary index as a percentage from control in the four groups. Data are presented as the mean ± standard deviation. One-way analysis of variance with Kruskal–Wallis multiple comparison test was used to compare groups. **p* < 0.05; ***p* < 0.01; ****p* < 0.001. SEV/REM (black column), SEV (grey column), DES/REM (blue column), PRO/REM (red column)

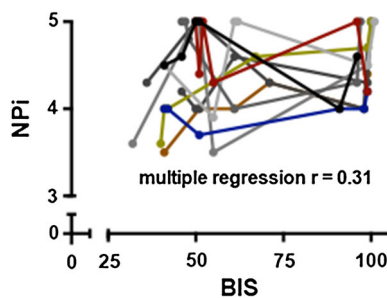
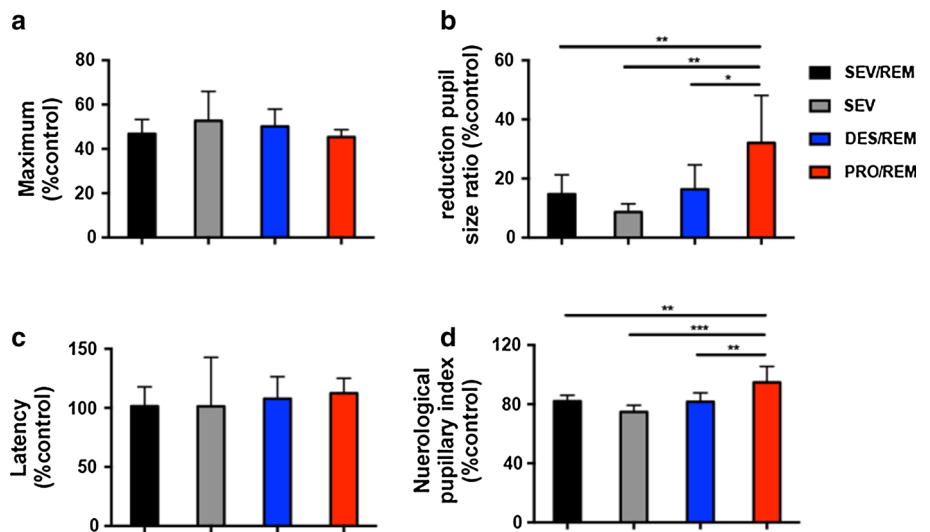


Fig. 2 Bispectral index (BIS) was measured at the same time as the neurological pupil index (NPI) in the PRO/REM group. Each data point represents a possible correlation between BIS and NPI measured in the PRO/REM group at each time point. Multiple regression to compute the regression coefficients based on an individual regression for each patient. Lines were connected dots belong to same patient

pupil and the %CH, but did not alter the NPi (Tables 2, 3, 4, 5). There was no significant correlation between the NPi and BIS (Fig. 2, *r* = 0.31, not significant).

4 Discussion

The effects of some anesthetic agents on pupillary reactivity have previously been reported [9, 10], but this is the first study to compare the effects of sevoflurane, desflurane and propofol on NPi and pupillometry parameters during surgery. It was reported that remifentanyl given in large doses that produced apnea altered the size of the pupil but produced on a minimal depression of the NPi [8]. We also found that fentanyl did not alter the NPi or latency of the

Table 2 The effects of anesthetics on MAX

Maximum (mm)	Control		Fentanyl		LOC		Intubation		Surgery		Recovery	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
SEV/REM	4.1	0.4			2.3****	0.3	2.2****	0.4	1.9****	0.2	2.9****	0.3
SEV	4.3	0.6							2.2*	0.4	3.2*	0.2
DES/REM	3.8	0.4	2.9***	0.1	2.4**	0.6	2.0****	0.3	1.9****	0.3	2.9	0.9
PRO/REM	4.3	0.6			2.2****	0.4	2.1****	0.4	2.0****	0.2	3.1*	0.9

Data are presented as the mean values. Repeated measures one-way analysis of variance with Dunnett’s multiple comparison test was used to compare each time point with the control

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$

Table 3 The effects of anesthetics on %CH

Reduction pupil size ratio (%)	Control		Fentanyl		LOC		Intubation		Surgery		Recovery	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
SEV/REM	34.0	4.8			11.0***	5.7	12.0****	7.8	4.8****	1.3	20.8****	5.0
SEV	37.4	3.2							3.2****	0.8	21.2**	4.1
DES/REM	35.6	4.9	27.4**	6.6	11.9***	9.1	9.7****	6.3	5.9****	3.4	20.3**	6.4
PRO/REM	37.1	4.5			12.5****	5.5	13.0****	6.0	12.0****	6.5	26.0*	10.0

Data are presented as the mean values. Repeated measures one-way analysis of variance with Dunnett’s multiple comparison test was used to compare each time point with the control

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$

Table 4 The effects of anesthetics on Latency

Latency (s)	Control		Fentanyl		LOC		Intubation		Surgery		Recovery	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
SEV/REM	0.24	0.0			0.28	0.0	0.26	0.0	0.25	0.0	0.26	0.0
SEV	0.23	0.0							0.23	0.1	0.25	0.0
DES/REM	0.24	0.0	0.25	0.0	0.28**	0.0	0.25	0.1	0.26	0.0	0.26	0.0
PRO/REM	0.23	0.0			0.25	0.0	0.24	0.1	0.25	0.0	0.24	0.0

Data are presented as the mean values. Repeated measures one-way analysis of variance with Dunnett’s multiple comparison test was used to compare each time point with the control

** $p < 0.01$

Table 5 The effects of anesthetics on NPi

NPi	Control		Fentanyl		LOC		Intubation		Surgery		Recovery	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
SEV/REM	4.4	0.1			4.1**	0.3	4.1*	0.3	3.6****	0.1	4.4	0.1
SEV	4.5	0.2							3.4****	0.2	4.3	0.3
DES/REM	4.6	0.2	4.5	0.3	3.9**	0.4	4.0**	0.4	3.7****	0.3	4.5	0.2
PRO/REM	4.4	0.2			4.2	0.4	4.3	0.4	4.2	0.4	4.5	0.3

Data are presented as the mean values. Repeated measures one-way analysis of variance with Dunnett’s multiple comparison test was used to compare each time point with the control

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$

light reflex (Tables 4, 5), providing further evidence that opioids only reduce the extent of the light reflex amplitude by decreasing the mechanical range of the pupil [8]. We also found that fentanyl significantly decreased the MAX (from 3.80 ± 0.37 at baseline to 2.94 ± 0.09 , $p = 0.0002$; Table 2). The muscle relaxants pancuronium and vecuronium have been shown to have no influence on pupillary size or light reflex amplitude [11]. We administered rocuronium only once to facilitate intubation where necessary, and to avoid the unknown effects of rocuronium on pupil measurements; the absence of any residual neuromuscular blockade was confirmed using a neuromuscular monitor.

Fentanyl, sevoflurane, desflurane and propofol produced decreases in pupil size, but not the LAT. It has been reported that patients with stage 4 hepatic encephalopathy have a prolonged latency phase compared with normal controls and patients with less severe stage 2 or 3 encephalopathy [12]. Prolonged LAT therefore might indicate the presence of a potential neurologic disturbance. Taylor and colleagues have reported that LAT is prolonged in patients with elevated intracranial pressure [13]. Therefore, it appears that prolonged LAT during anesthesia may indicate the presence of a potential neurologic disturbance. However, the algorithm used to measure latency by the neurooptics pupillometer might not be precise enough to detect small changes in latency brought about by anesthetic agents [14].

The mean %CH and NPi in patients anesthetized with sevoflurane or desflurane were lower than those anesthetized with propofol at 1 h after surgery had commenced (Fig. 1). This finding suggests that either volatile anesthesia may have been deeper than that of propofol anesthesia, or that there are anesthetic-dependent differences in their effects on brain activity. Our data do not allow us draw any firm conclusions in this regard. Current methods of brain monitoring such as the BIS are not able to assure equal levels of anesthetic depth when comparisons are made between diverse anesthetic agents and methods that include opioids [15]. Our results show that a satisfactory anesthetic that prevented movement to skin incision could be conducted without muscle relaxants by using a combination of propofol and remifentanyl, and without a change in the pupillary light reflex as measured by the NPi. Furthermore, we administered propofol/remifentanyl in doses sufficient to depress the BIS to values below 50, a common endpoint to gauge anesthetic depth during total intravenous anesthesia [16] and were unable to uncover a depression of the light reflex as measured by the NPi (Fig. 2).

In our cohort, the NPi score recovered quickly to baseline after surgery in those anesthetized with a volatile agent, but the MAX and %CH did not. This suggests that the NPi may be a simple and non-invasive means of

detecting the presence of residual inhalational anesthetic agents, or an expanding intracranial lesion, when patients do not emerge from anesthesia as quickly as expected.

5 Conclusions

Our primary findings are that the NPi decreased in the SEV/REM, SEV, and DES/REM groups, but not in the PRO/REM group. The NPi did not correlate with BIS. Taken together, these findings suggested that the NPi might have potential as a monitor to detect intracranial or mid-brain pathological processes even under the influence of anesthetic doses of propofol and remifentanyl.

Additionally our secondary findings are that fentanyl decreased the size of the pupil but did not alter NPi. NPi recovered quickly after surgery even when using volatile agents and the latency was not significantly altered by the anesthetic regimens.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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