Pupillometry-guided Intraoperative Remifentanil Administration *versus* Standard Practice Influences Opioid Use

A Randomized Study

Nada Sabourdin, M.D., Jérôme Barrois, M.D., Nicolas Louvet, M.D., Agnès Rigouzzo, M.D., Marie-Laurence Guye, M.D., Christophe Dadure, M.D., Ph.D., Isabelle Constant, M.D., Ph.D.

ABSTRACT

Background: Pupillometry has shown promising results for assessing nociception in anesthetized patients. However, its benefits in clinical practice are not demonstrated. The aim of this prospective randomized study was to evaluate the impact of intraoperative pupillometry monitoring on perioperative opioid consumption in major gynecologic surgery.

Methods: After receiving ethics committee approval and written consent of patients, American Society of Anesthesiologists status I to II women undergoing gynecologic surgery were included in this single-blinded, prospective, parallel-arm randomized study. General anesthesia was standardized with propofol–remifentanil target-controlled infusion. Patients were randomly assigned into two groups. In the pupillometry group, remifentanil administration was guided by pupillary diameter changes. In the standard group, remifentanil administration was left to the discretion of the anesthesiologist. The primary outcome was intraoperative remifentanil consumption.

Results: Fifty-five patients were analyzed. Remifentanil consumption was markedly decreased in the pupillometry group (3.8 [3.4 to 4.8 $\mu g \cdot kg^{-1} \cdot h^{-1}$] *vs.* 7.9 $\mu g \cdot kg^{-1} \cdot h^{-1}$ [6.5 to 9.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$] in the standard group; difference = 4.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ [95% CI, 3.0 to 5.3 $\mu g \cdot kg^{-1} \cdot h^{-1}$]; $P < 0.001$). Cumulative 0- to 12-h morphine consumption was reduced in the pupillometry group (two-way repeated measures ANOVA 0.3 ± 0.1 *vs.* 0.4 ± 0.2 mg/kg; $P = 0.048$). A telephone survey 3 months after surgery revealed that 15 of 29 patients in the standard group still experienced procedure-related pain *versus* 3 of 23 in the pupillometry group (chi-square $P = 0.037$). No adverse events associated with pupillometry were observed during the study.

Conclusions: The use of pupillometry to guide intraoperative analgesia reduced intraoperative remifentanil consumption and postoperative morphine requirements. The possible consequences of decreasing intraoperative remifentanil in terms of chronic pain require further investigation. **(Anesthesiology 2017; 127:284-92)**

THE monitoring of nociception is currently one of the major challenges in anesthesiology. Insufficient analgesia can lead to potentially deleterious hemodynamic variations. Conversely, the amount of administered opioids is related to the incidence of general side effects, such as respiratory depression, nausea, pruritus, or urinary retention. The amount of intraoperative remifentanil is also related to the incidence of postoperative remifentanil-induced hyperalgesia, which in turn might be associated with chronic pain.[1,2] Therefore, it is important to determine the minimal effective intraoperative opioid dose for each patient. Clinical parameters such as heart rate or blood pressure changes are currently used to assess intraoperative analgesia. Because these parameters are of questionable reliability and specificity under many circumstances, other physiologic indices or measures may be useful to provide more accurate clinical feedback regarding the level of analgesia. Several noninvasive devices have been investigated and commercialized during the past 10 yr, with different physiologic approaches and substrates, to monitor the intraoperative balance between nociception and antinociception. Their intended goal is to individually customize the intraoperative dose of opioids, avoiding both underdosage and overdosage.[3] Among these recent devices, pupillometry

What We Already Know about This Topic

- Since the days of ether, pupil diameter has been used to assess depth of anesthesia and guide anesthetic dosing
- Objective measurement of pupil diameter to guide intraoperative opioid dosing has not been assessed

What This Article Tells Us That Is New

- Objective pupil measurements were used to guide intraoperative remifentanil dosing in order to maintain postinduction pupil diameter
- In a randomized study, compared with standard approaches, patients in whom remifentanil dosing was pupillometry guided received 50% less intraoperative remifentanil and needed slightly less postoperative patient-controlled analgesia morphine

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appears to be a reliable tool. Pupillary diameter increases in response to nociceptive stimuli. This phenomenon is called "pupillary reflex dilation" and is observed in awake and anesthetized patients. The amplitude of pupillary reflex dilation is proportional to the intensity of nociceptive stimuli and inversely proportional to the amount of administered opioids.[4–7] In fact, during surgery, pupillary diameter is a dynamic function of the intensity of surgical stimuli and opioid dosage. However, no study has evaluated the potential clinical benefits of pupillometry-guided intraoperative analgesia. We hypothesized that remifentanil administration guided by pupillary diameter measurement would result in a difference in total intraoperative remifentanil consumption compared with standard practice. Therefore, we designed a randomized trial to investigate opioid requirements when intraoperative analgesia is guided by pupillometry compared with standard practice in women presenting for elective gynecologic surgery.

Materials and Methods

This was a prospective, single-blinded, pilot study approved by our institutional review board at St. Antoine Hospital (Paris, France; approval No. 10816). Recruitment took place between November 2010 and December 2012. Written informed consent was obtained for each patient. This study is registered with clinicaltrials.gov identifier NCT02576600. It was conducted in a single center, at Armand Trousseau Hospital (Paris, France).

We included women aged from 18 to 60 yr, American Society of Anesthesiologists (ASA) status I to II, scheduled for a gynecologic surgery under general anesthesia, with an expected procedural duration of at least 60 min. We excluded patients with chronic pain or preoperative analgesic or neuroleptic medication; patients with any history of substance abuse or psychiatric disease; patients with any ophthalmologic, neurologic, or metabolic disease; and patients under medications that could interfere with the autonomous nervous system (*e.g.*, β blockers).

After inclusion, patients were randomly assigned in parallel arms: one pupillometry group, and one standard group. Randomization sequence was achieved *via* a computer-generated list, by blocks of eight subjects, in a 1:1 ratio. An opaque sealed envelope containing the allocation group of the patient was inserted into her medical file. The investigator discovered the group to which the patient was allocated by opening the envelope on the day of surgery, before entering the operation room.

All of the patients received an oral premedication of 1 mg/kg of hydroxyzine, 1 h before the procedure. Standard monitoring included heart rate, blood pressure, oxygen saturation, neuromuscular blocking agents monitoring (TOF watch; Spacelabs Healthcare, USA), bispectral index (BIS; Covidien, Ireland), inspired and expired oxygen and carbon dioxide fractions, and central temperature. Pupillary diameter measurements were performed with the video pupillometer Algiscan (ID Med, France). This noninvasive device allows pupillary diameter measurement *via* an infrared camera that recognizes and tracks the pupil. The Algiscan includes an opaque rubber cup that surrounds the measured eye. The video pupillometer never touches the eye. Every measure requires holding the eyelid open for approximately 5 s (1 s to open the eyelid, 3 s to correctly position the device and press the "measure" button, and 1 s to close the eyelid), then the eye is closed again until the next measure. The measures are instantaneous pupillary diameters; they are not averaged over any period of time. In this study, no standardized stimulation, such as a calibrated tetanus, was applied to the patient before the measures.

Anesthesia was induced by effect-site target-controlled infusion (Base Primea; Fresenius-Kabi, Germany) of propofol and remifentanil. Using the Schnider model, the initial effect-site target concentration (Ce) of propofol was set at 6 μg/ml. Using the Minto model, the initial remifentanil Ce was set at 4 ng/ml. After a bolus of 0.5 mg/kg of atracurium, patients were intubated. After intubation, remifentanil Ce was set at 3 ng/ml. Propofol Ce was adjusted after intubation to maintain the BIS value between 40 and 60 throughout the procedure. Ventilation (50% oxygen and 50% air) was adjusted to maintain end-tidal carbon dioxide between 35 and 45 mmHg. If the train-of-four induced more than one response before the beginning of wound closure, a bolus of 0.25 mg/kg of atracurium was injected. Baseline values for heart rate, blood pressure, and pupillary diameter were recorded when the surgeon was ready to begin the procedure, at least 10 min after tracheal intubation, under stable general anesthesia, before any surgical stimulation.

For remifentanil management, patients were randomly assigned in two groups. In the standard group, intraoperative remifentanil Ce was left to the discretion of the anesthesiologist in charge of the patient, according to his usual practice. In our institution, pupillometry is not part of standard practice; therefore, in this group, pupillary diameter was measured every 5 min by a separate independent investigator who had no input on clinical management. The anesthesiologist in charge of the patient was blinded to the results of pupillary diameter measurements. In the pupillometry group, intraoperative remifentanil Ce was adapted every 5 min based on the variation in pupillary diameter. If pupillary diameter was increased by more than 30% compared with baseline (before skin incision), remifentanil concentration was increased by 0.5 ng/ml. If pupillary diameter was increased by 5 to 30% compared with baseline, remifentanil concentration was not modified. Finally, if pupillary diameter remained within 5% of baseline, remifentanil concentration was decreased by 0.5 ng/ml. The lower limit of remifentanil concentration allowed in the protocol was 1 ng/ml.

Several safety items for hemodynamic changes were added to our algorithm to manage a possible discrepancy between the changes in pupillary diameter and hemodynamic variations. In the pupillometry group, if blood pressure increased by more than 20% compared with baseline with a less than 30% increase in pupillary diameter, patients received intravenous boluses of 1 mg/kg of nicardipine. Conversely, if blood

pressure dropped by more than 30% with a pupillary dilation greater than 5% of baseline, patients received 500 ml of lactated Ringer's solution and intravenous boluses of 3 mg of ephedrine until blood pressure was restored. Finally, if heart rate decreased to less than 50 beats/min, remifentanil Ce was decreased by 0.5 ng/ml, whatever the size of the pupil.

For all of the patients, the first measurement was made under general anesthesia, just before skin incision, to determine baseline parameters. Subsequent measures were made every 5 min until wound closure; for example, during a 3-h surgery, 37 measurements were made. At the time of each measurement, the following additional data were manually reported on the dedicated data collection sheet: heart rate, blood pressure, temperature, BIS, propofol Ce, remifentanil Ce, and pupillary diameter. Sterile saline ophthalmic instillations were performed every 60 min for all of the patients.

In both groups, patients received 15 mg/kg of intravenous paracetamol and a bolus of 0.1 mg/kg of intravenous morphine 20 min before the end of the procedure. Remifentanil was stopped at the completion of wound closure. In the recovery room, intravenous morphine was titrated by administering 0.05 mg/kg boluses every 5 min until the visual analog scale (VAS) score was under 4/10. Then, morphine administration was managed by a standardized patient-controlled analgesia device with boluses of 1 mg, a refractory period of 6 min, and a maximal dose of 40 mg per 4 h. All of the patients received 15 mg/kg of scheduled intravenous paracetamol every 6 h for 24 h. Pain assessments were performed every 2 h during 8 h, then at the twelfth hour after the end of surgery. If the VAS score was greater than 3/10 despite morphine and paracetamol analgesia, patients received nefopam 20 mg IV every 6 h as necessary. If VAS score remained greater than 4/10, patients received ketoprofen 50 mg IV every 6 h as needed. Twenty-four hours after surgery, patients were asked to rate their overall satisfaction with pain management on a 4-point scale (0 = not satisfied at all, 3 = very satisfied). Patients were also interviewed using a standard set of questions to detect possible intraoperative awareness. We scheduled a telephone interview with each patient 3 months after the procedure to assess for the presence of persistent pain related to the surgery. All of the patients agreed to these postoperative interviews before inclusion in the study.

The main outcome measure was the total intraoperative remifentanil consumption. In addition, we analyzed propofol consumption, postoperative morphine requirements, and pain scores (VAS) from the recovery room until the twelfth hour after the end of surgery. Intraoperative data included anesthetic duration, number of remifentanil Ce modifications, baseline pupillary diameter, mean heart rate and blood pressure, ephedrine or nicardipine injections, and time to emergence (defined by the time between remifentanil discontinuation and extubation). Postoperative data included the need for nefopam and ketoprofen rescue analgesia, potential awareness, and patient's overall satisfaction before discharge. We also recorded the incidence of opioid-related side effects (nausea, vomiting, pruritus, urinary retention, and respiratory depression), and any ophthalmologic complication occurring within 12 h postoperatively. Finally, the persistence of any pain related to surgery 3 months after the procedure was recorded. No changes to the original protocol were made during the course of the study.

Statistical Analysis

The primary endpoint in this study was the remifentanil dose administered during surgery. Based on previous studies[8,9] investigating the influence of monitoring nociception in guiding perioperative opioid administration, the sample size was calculated to detect a difference of means of 25% with an expected SD within groups of 30%. A sample size of 24 patients was selected for each group, calculated by the Student's *t* test, with a level of significance of 0.05 and a power of 0.8. We estimated a 30% dropout, resulting in the final enrollment of 32 patients in each group (total 64 patients).

Statistical analysis was performed using XLSTAT 2011.4.04 (Addinsoft, France). The normal distribution of the continuous data was first evaluated using the Kolmogorov–Smirnov test. The normally distributed data were analyzed using the Student's *t* test. The nonnormally distributed and nonparametric data were analyzed using the Mann–Whitney U test. The Mann–Whitney U test was used to analyze the intraoperative remifentanil consumption and patient satisfaction. For the primary outcome, the 95% CI of the median difference was calculated with the method described by Bonett and Price.[8] The Student's *t* test was used to compare the mean values of intraoperative propofol consumption, baseline pupillary diameters, BIS values, emergence times, hemodynamic data, and the postoperative cumulative 0- to 12-h morphine consumption. Chi-square tests were used to compare the frequency of nicardipine injections, nausea, the number of patients requiring rescue analgesia by nefopam or ketoprofen, and the number of patients still reporting pain after 3 months. Fisher exact test was used to compare the frequency of ephedrine injections, as well as postoperative pruritus. Postoperative pain scores up to 12 h after surgery were analyzed using two-way repeated-measures ANOVA. The relationship between intraoperative consumption of remifentanil and postoperative morphine requirement was assessed with a covariance analysis (ANCOVA). For this ANCOVA, the outcome was postoperative cumulative 0- to 12-h morphine consumption, the predictor was the group, and the covariate was intraoperative remifentanil consumption. This analysis was developed *post hoc*. The relationship between baseline pupillary diameter and baseline BIS, as well as the relationship between baseline pupillary diameter and baseline propofol Ce, were investigated using the Spearman rank correlation test.

Data are expressed as mean ± SD, median (25th to 75th percentiles), or number of patients (percentage). *P* values

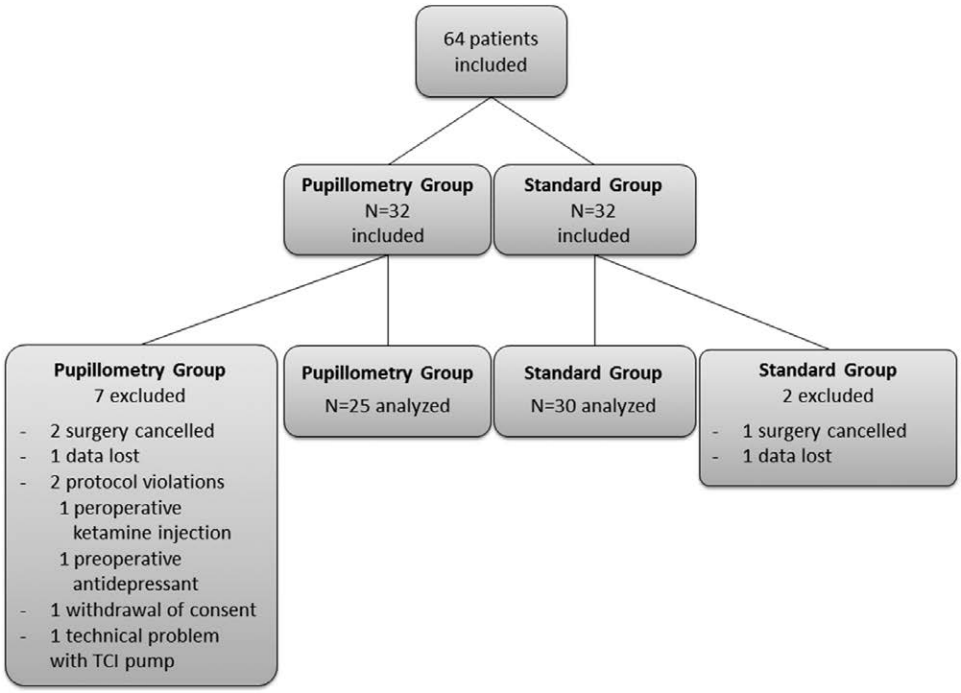

Fig. 1. Flow chart.

Table 1. Demographic Data

Variable	Pupillometry	Standard
No. of patients	25	30
Age (yr)	46 ± 8	44 ± 8
Weight (kg)	68 ± 14	66 ± 14
Height (cm)	166 ± 6	163 ± 6

were reported as two-tailed values, and a P value less than 0.05 was considered statistically significant.

Results

Sixty-four patients were included in the study. Nine patients were secondarily excluded; thus, data were analyzed for 25 patients in the pupillometry group and 30 patients in the standard group. Details are given in the flow chart provided in figure 1. Demographic data were similar in both groups (table 1). A total of 1,536 measurements were performed during the study, including 810 measures on the 30 patients in the standard group and 726 measures on the 25 patients in the pupillometry group.

Intraoperative data are detailed in table 2. Remifentanil consumption was markedly decreased in the pupillometry group as compared with the standard group (3.8 [3.4 to 4.8 $\mu g \cdot kg^{-1} \cdot h^{-1}$] *vs.* 7.9 $\mu g \cdot kg^{-1} \cdot h^{-1}$ [6.5 to 9.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$]; difference = 4.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ [95% CI, 3.0 to 5.3 $\mu g \cdot kg^{-1} \cdot h^{-1}$]; Bonett and Price $P < 0.001$; fig. 2). Propofol consumption was similar in both groups (8.5 ± 1.1 *vs.* 8.8 ± 1.3 mg · $kg^{-1} \cdot h^{-1}$; Student's t test $P = 0.34$; fig. 2). The number of changes in remifentanil Ce was similar in both groups. Individual evolution of remifentanil Ce is given for every patient in figure 3. Baseline pupillary diameter was similar in both groups. The range of baseline pupillary diameters was 1.5 to 2.4 mm in the standard group and 1.5 to 2.3 mm in the pupillometry group. Mean intraoperative heart rate and blood pressure were similar in both groups. Mean duration of anesthesia and time to emergence were similar in the standard and pupillometry groups. Eleven patients in the pupillometry group received a bolus of nicardipine but none in the standard group. There was no difference in ephedrine requirement between the standard and pupillometry groups. The correlation coefficients between the baseline pupillary diameters and either the BIS value or propofol Ce were of moderate sizes and did not reach statistical significance (Spearman, respectively, $r = 0.20$, $P = 0.15$ and $r = 0.22$, $P = 0.13$).

Postoperative data are detailed in table 3. Cumulative 0- to 12-h morphine consumption was reduced in the pupillometry group as compared with the standard group (0.3 ± 0.1 *vs.* 0.4 ± 0.2 mg/kg; Student's t test $P = 0.048$; fig. 2). There was a significant linear correlation between the intraoperative remifentanil consumption and postoperative cumulative 0- to 12-h morphine consumption (ANCOVA $r = 0.38$; $P = 0.005$; fig. 4). Postoperative pain levels were low. VAS scores were not statistically different between either the two groups or between the different time points (ANOVA $P = 0.95$ and $P = 0.37$, respectively; no interaction; fig. 5). Rescue analgesic requirements were similar in both groups. The incidence of opioid-related side effects was similar in both groups. No urinary retention or respiratory depression was observed. No ophthalmic complications occurred. No awareness was

Table 2. Intraoperative Data

Variable	Pupillometry (N = 25)	Standard (N = 30)	*P* Value
Duration of anesthesia (h)	3.1 ± 0.6	2.9 ± 0.8	0.30
No. of changes in remifentanil target concentration	4 ± 2	5 ± 2	0.33
Duration between intubation and baseline measurement (min)	31 ± 11	27 ± 11	0.21
Baseline pupillary diameter (mm)	1.9 ± 0.2	1.9 ± 0.2	0.74
Mean heart rate during surgery (beats/min)	67 ± 10	69 ± 11	0.57
Mean blood pressure during surgery (mmHg)	89 ± 12	85 ± 8	0.26
Patients requiring nicardipine, n (%)	11 (42.3)	0	< 0.001
Patients requiring ephedrine, n (%)	3 (11.5)	1 (3.3)	0.32
Mean bispectral index	40 ± 7	40 ± 8	0.72
Emergence time (min)	17 ± 7	15 ± 8	0.33

Data are mean ± SD unless otherwise specified.

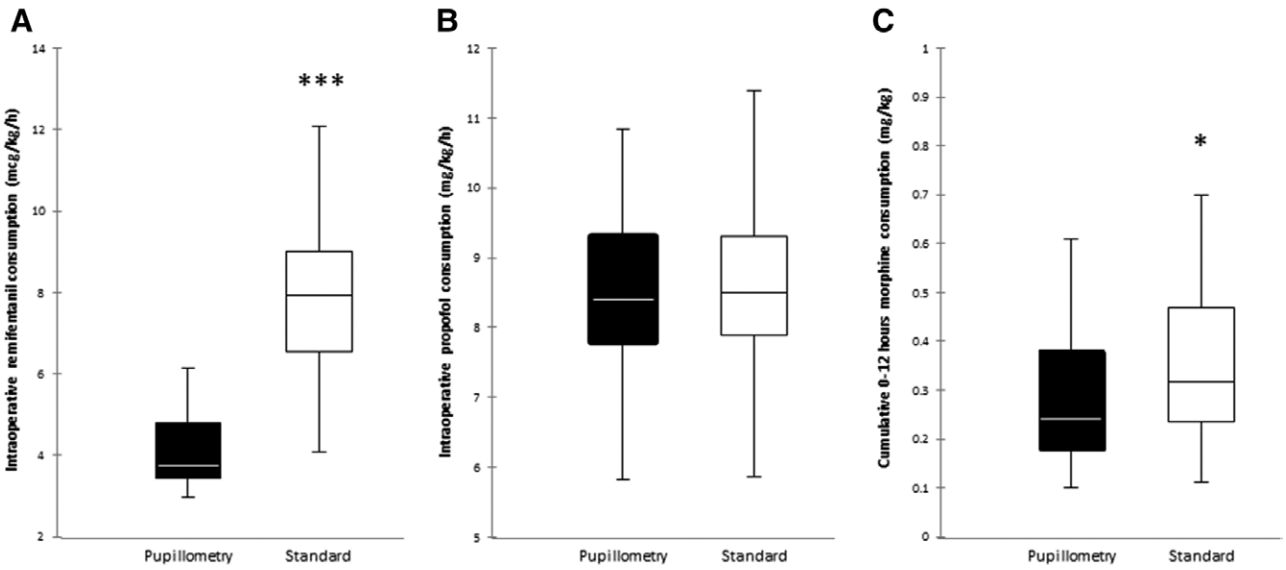

Fig. 2. (*A*) Intraoperative remifentanil consumption: median (25th to 75th percentile), range. (*B*) Intraoperative propofol consumption: median (25th to 75th percentile), range. (*C*) Postoperative cumulative 0- to 12-h morphine consumption: median (25th to 75th percentile), range. **P* < 0.05. ****P* < 0.001.

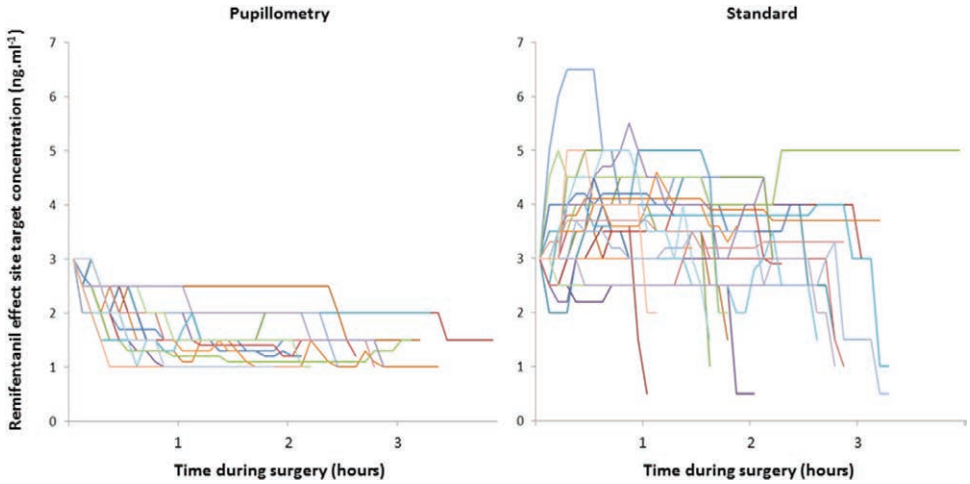

Fig. 3. Individual evolution of remifentanil effect-site target concentration in the pupillometry (*25 lines*; left) and standard groups (*30 lines*; right). Each *line* represents a patient.

Table 3. Postoperative Data

Variable	Pupillometry (n = 25)	Standard (n = 30)	*P* Value
Patients requiring nefopam, n (%)	20 (80)	25 (83)	0.94
Patients requiring ketoprofen, n (%)	12 (48)	13 (43)	0.99
Postoperative nausea or vomiting, n (%)	9 (36)	13 (43)	0.78
Pruritus, n (%)	1 (4)	0	0.46
Suspected awareness, n (%)	0 (1 reported dreaming)	0	—
Patient satisfaction, median (25th to 75th percentile)	3 (2–3)	2 (1–3)	0.054

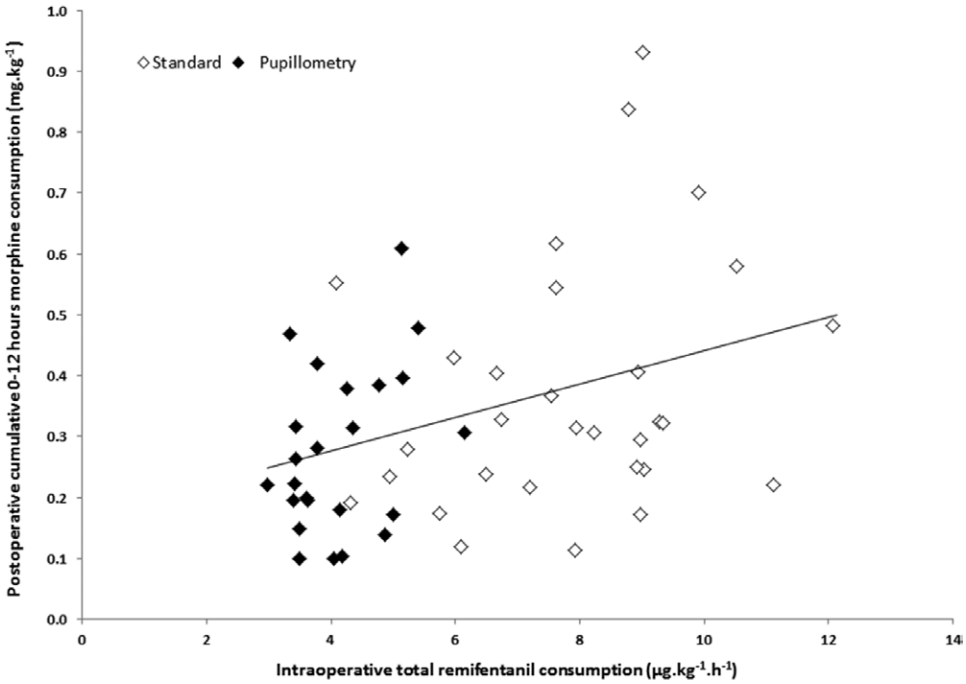

Fig. 4. Relationship between total intraoperative remifentanil consumption and cumulative 0- to 12-h postoperative morphine consumption. Each *point* represents a patient. *Black squares* represent patients from the pupillometry group and *white squares* represent patients from the standard group. After testing for homogeneity of covariance, the *solid line* represents the correlation between intraoperative remifentanil consumption and cumulative 0- to 12-h postoperative morphine consumption in both groups. ANCOVA r = 0.38; *P* = 0.005.

suspected in any patient. Median patient satisfaction regarding pain management during their hospital stay was 3 in the pupillometry group and 2 in the standard group.

Three months after the procedure, one patient in the standard group and two in the pupillometry group did not answer our repeated telephone calls. In the standard group, 15 of 29 responding patients still reported pain related to the procedure *versus* 3 of 23 in the pupillometry group (chi-square test *P* = 0.004; fig. 5). Symptoms were described either as deep abdominal or pelvic pain or superficial pain close to the surgical wound.

Discussion

In women anesthetized by propofol and remifentanil target-controlled infusion, we demonstrated a marked reduction in intraoperative remifentanil consumption when pupillometry was used to guide remifentanil Ce compared with standard practice. This intraoperative reduction of remifentanil was further associated with lower postoperative morphine requirements during the 12 h after emergence.

The standard management of remifentanil relies mainly on appreciation of hemodynamic variations. Indeed, a nociceptive stimulation induces an autonomic response, characterized by an increase in sympathetic activity and a decrease in parasympathetic activity, both resulting in an increase in heart rate and blood pressure. However, under general anesthesia, these hemodynamic responses may be modified by interfering physiopathologic processes, such as hypovolemia, laparoscopic pneumoperitoneum, or concomitant drug therapies. By contrast to this approximate assessment of nociception, more and more reasons have emerged to be rigorous regarding the doses of intraoperative opioids. Insufficient analgesia is known to be deleterious by increasing the blood level of stress hormones, for example leading to tachycardia or hypertension. Excessive intraoperative remifentanil administration, in contrast, might lead to increased postoperative

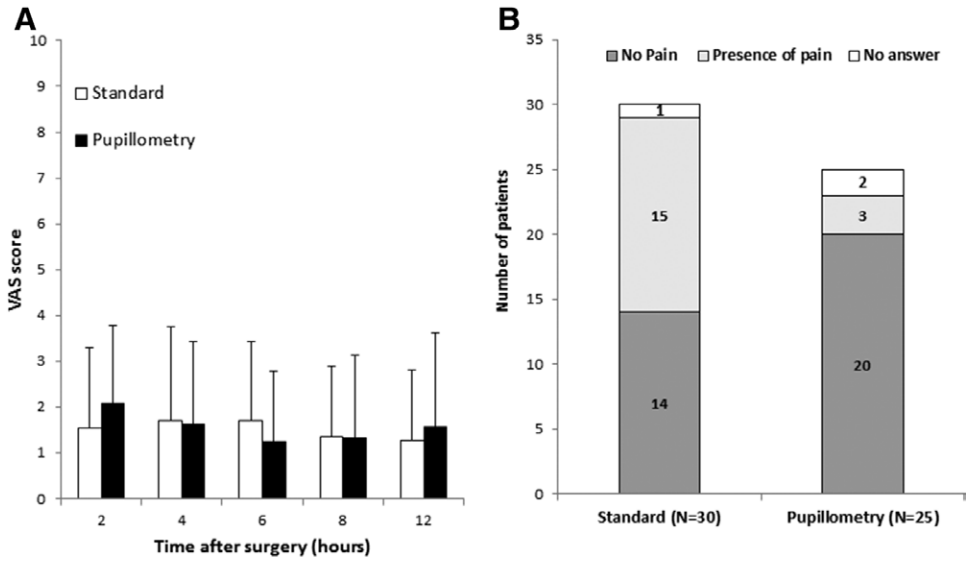

Fig. 5. Postoperative pain. (*A*) During the first 12 h, by visual analog scale (VAS), in the pupillometry (*black*) and standard (*white*) groups: mean, SD. (*B*) Three months after procedure, by telephone survey. *Light gray* indicates number of patients who reported persistent pain; *dark gray* indicates number of patients who reported no persistent pain; and *white* indicates number of patients who did not answer our phone calls.

morphine requirements, a phenomenon described by some authors as remifentanil-induced hyperalgesia.[2]

Pupillometry is one of the devices commercialized for the assessment of intraoperative nociception.[3] However, no study has investigated a potential clinical benefit associated with its use. The main problem seems to be determining the clinically relevant thresholds of pupillary dilatation to characterize insufficient or excessive analgesia. In our study, the choice of the percentage of pupillary dilatation leading to changes in remifentanil Ce was a major issue. A recent study reported that, in awake patients, a pupillary dilation of 23% predicted a verbal pain score of more than 1 on a 4-point scale with 91% sensitivity and 94% specificity.[7] In addition, in a preliminary study, we have found in children anesthetized with ketamine that movement in response to nociceptive stimulation was associated with pupillary dilation of more than 32% (N. Sabourdin, M.D., I. Constant, Ph.D., Department of Anesthesia, Armand Trousseau Hospital, Paris, France; personal data). Based on these findings, we established the threshold of pupillary dilatation for remifentanil Ce increase to be 30%. The Algiscan has a precision of 0.1 mm, corresponding with 5% of a 2.0-mm baseline diameter. Therefore, we considered the pupillary response to be insignificant when less than 5%, allowing a decrease in remifentanil Ce.

Pupillometry is not the first monitor that was tested to guide remifentanil infusion. The Surgical Pleth Index (SPI; General Electric, USA) was also evaluated in two studies on patients anesthetized with propofol and remifentanil, which both demonstrated a decrease in intraoperative remifentanil consumption when the SPI was used to guide analgesic administration compared with standard practice.[9,10] These findings, taken together with our results, suggest that intraoperative assessment of the nociception–antinociception balance might help anesthesiologists tailor opioid administration to each patient's individual requirements. Thus, it might become possible to administer the minimal necessary amount of analgesics to each patient.

The mean remifentanil consumption observed in the standard group was consistent with data reported in other studies involving total intravenous anesthesia with propofol and remifentanil in patients undergoing gynecologic surgery.[11,12] Our design prioritized pupillary diameter changes over hemodynamic variations; consequently, the administration of nicardipine was more frequent in the pupillometry group. No adverse hemodynamic effects were observed as a result of this management. Remifentanil and propofol act synergistically on the depth of anesthesia, but, interestingly, despite the low concentrations of remifentanil reached in the pupillometry group, no patient reported features suggesting awareness.

Pupillometry-guided remifentanil administration did not result in more frequent remifentanil Ce adaptations. The difference in total remifentanil consumption seems related not to the number of changes but rather to the direction and amplitude of these changes (fig. 3). In the pupillometry group, most changes were remifentanil Ce 0.5 ng/ml decreases, whereas, in the standard group, changes were bidirectional (increases or decreases), and their amplitude was sometimes greater than 0.5 ng/ml.

Pupillary diameter is under dual sympathetic/parasympathetic control: sympathetic output causes pupillary dilation, and parasympathetic output causes constriction. In awake subjects, pupillary dilation in response to painful stimulation is primarily mediated by sympathetic activation. However, in anesthetized humans, pupillary dilation seems to be

primarily caused by an inhibition of the parasympathetic pathways from the Edinger–Westphal nucleus.[13] Under anesthesia, the reflex dilation of the pupil might be mediated by noradrenergic inhibition of the preganglionic parasympathetic neurons in the Edinger–Westphal nucleus, with little contribution from the direct sympathetic pupillary pathway.

Opioids directly affect pupillary diameter. By decreasing the inhibitory control over the Edinger–Westphal nucleus, opioids increase the activity of the efferent parasympathetic pathway between the Edinger–Westphal nucleus and the pupil, leading to a contraction of the circular sphincter of the iris.[14] In our study, we adapted remifentanil Ce to pupillary diameter variations. It is of course very likely that part of these pupillary diameter variations were determined by variations in remifentanil plasma concentration through the direct action of opioids on the pupil. However, if pupillary diameter results in part from the amount of opioids, it also depends on the intensity of the nociceptive stimulation to which the patient is exposed. Because of this double dependence (amount of opioids and nociceptive intensity), we consider that pupillary diameter under general anesthesia characterizes the balance between nociception and antinociception rather than a simple surrogate measure of opioid effect on the pupil.

In our study, we did not apply standardized nociceptive stimuli, such as calibrated tetanus, to assess pupillary reflex dilation. Because we wanted to test the potential benefits of pupillometry in clinical practice, we chose to consider surgery as the nociceptive stimulus determining pupillary dilation. The level of nociception induced by surgery varies over time. Some surgical stages are particularly intense (*e.g.*, skin incision, hysterotomy), whereas others are less so (*e.g.*, tubal ligation, wound closure). To keep the nociception–antinociception balance at equilibrium, we should be able to adapt our intraoperative analgesia to the individual instantaneous needs of the patient. In the future, monitors such as the pupillometer (or the SPI,[9,10] the Analgesia–Nociception Index,[15] or more recent devices, such as the Nociception Level Index[16]) might help us achieve this goal.

The analysis of baseline pupillary diameters provides interesting data about the interindividual variability of remifentanil effects on pupillary diameter. Baseline pupillary diameter varied within a wide range in our population, and neither concomitant BIS value nor propofol Ce could account for this variability. One remaining possible explanation of this phenomenon could be the interindividual sensitivity to opioids. These results confirm the relevance of individualized customization of intraoperative opioid administration.

The relationship between intraoperative remifentanil consumption and postoperative morphine requirements has been questioned by numerous authors. Indeed, it seems that, for similar procedures, higher intraoperative remifentanil consumption is associated with higher postoperative opioid requirements.[17,18] This phenomenon is currently attributed to the development of remifentanil-induced hyperalgesia.[2] The first short-term consequence of remifentanil-induced hyperalgesia after surgery is the increase in postoperative morphine requirements, potentially leading to an increased incidence of side effects. In our study, despite a significant difference in postoperative morphine consumption, we failed to demonstrate any difference regarding side effects. That may be explained by insufficient statistical power: indeed, our population size was calculated from our primary outcome, which was remifentanil consumption. Another possible association with remifentanil-induced hyperalgesia is the persistence of pain at the surgical site, with the potential risk of chronic pain development. This association has already been suggested by De Kock *et al.*[19] in adults undergoing major colorectal surgery. Three months after surgery, women from the standard group reported persistent pain more frequently than those from the pupillometry group. However, the interpretation of these results is subject to serious limitations: the incidence of chronic pain was not our primary outcome, and we did not use a validated chronic pain questionnaire during the telephone interview. Further investigation is required to more precisely characterize the persistent pain and whether its incidence may be reduced by a decrease in intraoperative opioid consumption.

There are several other limitations to our study. We only included relatively young and healthy patients, without cardiovascular disease, so our results cannot be extrapolated to older or more fragile patients. In addition, whether pupillary guidance of analgesia reduces opioid consumption when different concomitant anesthetic agents are used needs to be demonstrated.

Baseline pupillary diameter was obtained by a single instantaneous measurement. The individual thresholds of 5 and 30% would have gained in precision and accuracy if baseline diameter had been averaged over several measures. In addition, because of this single baseline measurement, our study does not allow the assessment of intraindividual variability of pupillary diameter in the absence of nociceptive stimulation.

It was not possible, in practice, to standardize ambient light for all measurements. Thus, pupillary diameters might have been influenced by ambient light during the 1 to 2 s between eyelid opening and light occlusive pupillometer placement. However, this potential bias applies to the measures for all patients in both groups (1,536 measures). It is unlikely that this possible confounding factor alone accounts for the very significant difference in remifentanil consumption between the groups.

Finally, in our protocol, we used pupillary size alone to guide remifentanil administration. A monitoring system combining different approaches of nociception (*e.g.*, sympathetic, parasympathetic, central, peripheral) would probably provide the best results for guiding intraoperative analgesia. Our study does not recommend pupillometry as a sole monitoring device to guide intraoperative analgesia; its goal is rather to validate pupillary diameter as one relevant index in this indication.

In conclusion, we have demonstrated that it was possible to significantly reduce intraoperative remifentanil

consumption when pupillometry was used to guide remifentanil administration compared with standard practice. In addition, cumulative 0- to 12-h postoperative morphine consumption was also reduced. This decrease in remifentanil and morphine consumptions was not associated with any evidence of perioperative opioid underdosage.

Our results suggest that the reduction of intraoperative remifentanil consumption might become an important endpoint for improving the global analgesic management of surgical patients. Further studies are required to confirm our results and any possible benefits in terms of chronic pain after surgery.

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Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available at: nada.sabourdin@aphp.fr. Raw data available at: nada.sabourdin@aphp.fr.

Correspondence

Address correspondence to Dr. Sabourdin: Département d'Anesthésie, Hôpital Armand Trousseau, 26 Avenue du Dr Arnold Netter, 75012 Paris, France. nada.sabourdin@aphp.fr.

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