Pupillometry to detect pain response during general anaesthesia following unilateral popliteal sciatic nerve block

A prospective, observational study

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CONTEXT Pupillary reflex dilation appears to be a reliable indicator of response to noxious stimulation even under general anaesthesia. The ability of pupillometry to detect the effects of extremity blocks during continuous infusion of opioids remains unknown.

OBJECTIVE To explore the performance of pupillometry to detect differences in pupillary reflex dilation response to a standardised noxious stimulus applied to each leg following unilateral popliteal sciatic nerve block during continuous infusion of remifentanil.

DESIGN Prospective, observational study.

SETTING University hospital anaesthesia department, between June 2010 and December 2010.

PATIENTS Twenty-four adult patients undergoing elective foot or ankle surgery under general anaesthesia who requested a peripheral nerve block. Unilateral popliteal sciatic nerve block with 0.75% ropivacaine and 1% lidocaine was performed awake. General anaesthesia was maintained with steady-state infusions of propofol and remifentanil.

MAIN OUTCOME MEASURE Video-based pupillometer was used to determine pupillary reflex dilation during tetanic stimulation (60 m, 100 Hz) applied to the skin area innervated by the sciatic nerve for 5 s after the onset of general anaesthesia.

RESULTS Sensory nerve block led to a blunted maximal pupillary reflex dilation response to noxious stimulation compared with the non-blocked leg: median (interquartile range) change from baseline 2% (1 to 4%) versus 17% (13 to 24%), respectively ($P < 0.01$). The differences in the response persisted throughout the 5-s stimulus and the recovery phase.

CONCLUSION These results are a proof of concept. The effects of peripheral nerve block can be detected via the measurement of pupillary reflex dilation response to noxious stimulation of the skin in patients receiving remifentanil.

Published online xx month 2013

Introduction

Pupillary reflex dilation has been studied for nearly 20 years as a potential marker of response to noxious stimulation in volunteers and surgical patients. In response to an incision or tetanic electrical stimulation of the skin, pupillary reflex dilation monitoring permits the detection of a dramatic increase in pupil size, even during general anaesthesia.\(^1\)\(^-\)\(^4\) Marked differences in pupil size and reactivity have also been found following the noxious stimulation of centrally blocked and non-blocked segments during combined epidural and general anaesthesia.\(^3\)\(^-\)\(^8\) Moreover, pupillary reflex dilation was shown to be more sensitive when compared with other variables commonly used to assess response to noxious stimulation during general anaesthesia, such as heart rate and arterial blood pressure.\(^1\)\(^-\)\(^4\)

In all of the previous studies, no or very low doses of opioids were concomitantly administered. Importantly,
an inverse correlation has been shown between the amplitude of pupil reactivity and the dose of systemic opioids (alfentanil, remifentanil) with a substantial inhibition of stimulus-induced pupillary dilation being observed following moderate-to-high doses of opioids.9,10

The close dependency of pupil size measurements to the administration of opioids might be viewed as a limitation of the technique to monitor analgesia during general anaesthesia, in particular to assess the adequacy of regional blocks during opioid infusion. In addition, testing the efficacy of extremity blocks during general anaesthesia using pupillary reflex dilation measurements has been unexplored yet, as recently pointed out.11 In a proof-of-concept study, we measured the pupillary reflex dilation response to noxious stimuli in patients undergoing extremity surgery and receiving unilateral peripheral sensory nerve block and propofol–remifentanil anaesthesia. Our aim was to explore the performance of pupillometry to detect differences in pupillary reflex dilation response to a standardised noxious stimulus applied to each leg following unilateral popliteal sciatic nerve block during general anaesthesia, each patient acting as their own control.

Methods

This prospective observational study took place between June 2010 and December 2010 at the University Hospital of Grenoble. The Institutional Review Board of Sud-Est II (Chairperson Prof M. David, Hôpital Hotel-Dieu, Lyon, France) approved the design of the study on 3 June 2010 and waived the requirements for written informed consent from each patient (Ref#20110–016–2). Adult patients were prospectively enrolled in the study if they were scheduled for elective unilateral foot or ankle surgery under general anaesthesia, and expressed the desire for a peripheral nerve block as part of the postoperative pain management plan. Exclusion criteria were a known history of peripheral neuropathy in the lower extremities, coagulation disorders, known reaction to local anaesthetic agents, dysfunction of the autonomic nervous system in relation to advanced diabetes mellitus, systemic amyloidosis, multiple sclerosis and uncontrolled systemic hypertension, postoperative pupil abnormality, or concomitant treatment with opioids, metoclopramide or droperidol.12

Anaesthesia protocol

This study did not interfere with standard patient care nor the anaesthesia protocol used routinely for such patients. Patients received oral hydroxyzine 1 mg kg−1 and/or alprazolam 0.5 mg as premedication. Popliteal sciatic nerve block was performed using ultrasound guidance (Sonosite S-Series Sonosite Inc., Bothell, Washington, USA) with a lateral approach before the induction of general anaesthesia. A single bolus of 20 ml mixture of 1% lidocaine 10 ml and 0.75% ropivacaine 10 ml was administered using a 5 cm insulated needle inserted into the popliteal fossa above the separation of the sciatic nerve into the tibial and common peroneal nerve, as described previously.13

Once the peripheral block had been performed, general anaesthesia was induced without delay and maintained with target-controlled infusion (TCI) of propofol (Master TCI; Fresenius Kabi AG, Bad Homburg, Germany) and a continuous infusion of remifentanil (0.25 µg kg−1 min−1). Tracheal intubation was facilitated with cisatracurium (0.15 mg kg−1). Mechanical ventilation with oxygen 40% in air adjusted to maintain the end-tidal carbon dioxide at 4.0 to 4.6 kPa. After tracheal intubation, the propofol TCI was adjusted to maintain the bispectral index at approximately 40 (A-2000 BIS; Aspect Medical Systems Inc., Norwood, Massachusetts, USA). The remifentanil infusion dose was reduced to between 0.01 to 0.03 µg kg−1 min−1 after tracheal intubation, and adjusted to maintain the SBP and heart rate within 80 to 120% of preinduction values. Patients were kept warm throughout surgery using an air warmer device (Bair Hugger; Arizant Healthcare, Eden Prairie, Minnesota, USA) and a blanket.

On completion of pupillary reflex dilation measurements (see below), a calf tourniquet was inflated to 100 mmHg above SBP to permit surgical procedure.

To complement the sciatic nerve block, postoperative analgesia was achieved using paracetamol and ketoprofen. Both drugs were administered intravenously on completion of pupillary reflex dilation measurements. After tracheal extubation and transfer to the postanaesthesia care unit, patients were asked to self-rate their pain intensity at rest using a 10-cm visual analogue scale.

The number of patients requiring intravenous boluses of morphine to relieve pain (visual analogue scale scores >3 cm) was recorded. Patient response to a cold stimulus applied to the same skin territory as used for electrical stimulation (see below) was measured in the postanaesthesia care unit, and characterised as present or absent. Absence of cold sensation was considered as complete (successful) sensory block.

Determination of the pupillary reflex dilation

The pupillary reflex dilation was measured using a commercially available infrared portable pupillometer (Neurolight version 1.2; IDMed, Marseille, France) during steady-state anaesthesia (no change in propofol and remifentanil dose during measurements). The pupillometer incorporates a tetanic stimulus device allowing the synchronisation of noxious stimulus activation and pupillary reflex dilation recording. Pupil diameter was video-recorded (25 images per second) with an accuracy of 0.1 mm and a spatial resolution of 0.01 mm. A noxious tetanic stimulus (100 Hz, 60 mA) was applied for a 5 s to the skin innervated by the lateral sural cutaneous nerve, which originates from the common fibular nerve. Skin stimulation electrodes were placed 5 to 7 cm below the head of the fibula on the lateral side of
each leg and connected to the pupillometer, and then wrapped with a sterile sheet. All pupillary reflex dilation measurements lasted 2 min and were performed before surgery during steady-state anaesthesia. The non-invasive blood pressure, heart rate and bispectral index were recorded before and after the tetanic stimulus.

For pupil size evaluation, the upper lid of one eye was opened and the infrared pupillometer was applied with no contact with the cornea, sealing the eye from the ambient light. Each pupillary reflex dilation recording consisted of a sequence of 13 s with 325 serial pupil diameter measurements (25 images per second for 13 s): before the noxious stimulation (3 s, baseline), during tetanic stimulation (5 s, stimulus) and after stimulation (5 s, recovery). Pupil diameter was assessed while the patient remained in the dorsal position. The pupillary reflex dilation measurements were performed first during noxious stimulation of the blocked leg and then during stimulation of the non-blocked leg with a 60-s interval in between. On completion of the pupillary reflex dilation test, the eye was carefully closed. The contralateral eye remained covered during measurements.

Measurements of pupil diameter were automatically expressed as two variables: the minimum amplitude (Min) was the median value of 75 consecutive images acquired during the 3-s baseline period; and the maximum amplitude (Max) was the median value of 12 consecutive images including the largest pupil diameter acquired during the period ranging from 1 s after the start of tetanic stimulation to the end of the recording (Fig. 1). The pupillary reflex dilation response was then calculated: pupillary reflex dilation (% of baseline) = 100 × (Max−Min)/Min. In addition, pupil size changes over the entire pupillary reflex dilation recording period allowed the calculation of the area under the response curve (AUC

**Statistical analysis**

Variables were expressed as frequency and percentage, and median and interquartile range (IQR). The AUC

**Results**

We studied 24 consecutive patients during the study period. Table 1 shows their characteristics and anaesthesia-related data prior to tetanic stimulation. No patient received atropine or catecholamines. Patients maintained in steady-state anaesthesia showed no significant differences in SBP, heart rate or bispectral index on noxious stimulation of the non-blocked nerve territory compared with the prestimulation period: the median (IQR) change in SBP = 0 mmHg (−6 to +4); change in heart rate = −1 min⁻¹ (−4 to +4); and, change in bispectral index = 0 (−3 to +2).

Pupillary reflex dilation measurements were performed a median (IQR) of 45 min (35 to 62) after the nerve block placement and 29 min (26 to 39) after the induction of anaesthesia. This timing corresponded to a simulated median concentration of remifentanil of 0.75 ng ml⁻¹.
Initial pupil diameters prior to the noxious stimulus were comparable: 2.0 mm (1.8 to 2.4) from the blocked leg versus 1.9 mm (1.7 to 2.4) from the non-blocked leg (not significant). Marked differences in the response of pupil diameter were then measured following cutaneous electrical stimulation of sensory nerve blocked and non-blocked legs for all patients. Maximal pupil diameters were 2.0 mm (1.8 to 2.4) with stimulation of the blocked leg versus 2.3 mm (2.0 to 2.9) with the non-blocked leg ($P < 0.01$). This corresponded to a pupillary reflex dilation response of 2% (1 to 4) from baseline when the stimulus was applied to the blocked leg versus 17% (13 to 24) when applied to the non-blocked leg ($P < 0.01$; Fig. 2). The median difference in pupillary reflex dilation was 15% (11 to 22). Under our conditions, all but one patient had a pupillary reflex dilation response of more than 10% from non-blocked leg. This means that the pupillary reflex dilation threshold value corresponding to the unilateral sensory blockade was less than 10%, with 96 and 100% sensitivity and specificity, respectively.

The differences in the pupillary response between the two stimulated territories persisted throughout the stimulus and recovery phases (Fig. 3). Whereas pupil diameter increased rapidly after the start of tetanic stimulation of the non-blocked leg, reaching maximum values at 2 to 4 s, no change in pupil diameter was observed when the stimulus was applied to the blocked leg. The AUC$_0$ to $13_5$, corresponding to noxious stimulation of the non-blocked leg was higher than that of the blocked leg: 91% s (66 to 122) versus 0% s ($-16$ to 5), respectively ($P < 0.01$).

In the postoperative period, the response to a cold stimulus was assessed 130 min (98 to 204) after administering the sciotic nerve block. Successful blocks as defined by absent cold sensation in the blocked territory were found in all 22 assessed patients. The two patients in whom the cold sensation test was not performed reported no postoperative pain. Seventeen patients reported no pain at all in the postanaesthesia care unit (visual analogue scale measurements for pain of 0) and seven patients required a median dose of 10 mg (6 to 13) of morphine. Those patients had pain levels of 6 (5 to 8) using the visual analogue scale on arrival in the postanaesthesia care unit, which related to an extended or additional surgical procedure, such as bone graft harvested from the iliac crest, contralateral hallux valgus repair with popliteal sciatic nerve block performed postoperatively. No differences were found between the seven patients who reported pain and the 17 who did not, with regard to the type of surgery, quality and timing of sensory block, remifentanil dose or pupillary reflex dilation measurements.

**Discussion**

Our results are a proof of concept, and indicate that pupillary reflex dilation measurements during tetanic stimulation of the skin can perceive the effects of unilateral popliteal sciatic nerve block in patients receiving concomitant infusion of remifentanil in whom no systemic response to pain is reported. These peripheral blockade-induced differences in pupillary reflex dilation response may provide further evidence for the performance of pupillometry as a technique to accurately

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**Table 1** Baseline characteristics of the 24 patients and their anaesthesia-related data prior to tetanic stimulation

| Age; years | 49 (34 to 59) |
| Sex; (male/female) | 8/16 |
| Weight; kg | 64 (59 to 82) |
| BMI; kg m$^{-2}$ | 23 (21 to 28) |
| ASA physical status; (I/II) | 18/6 |
| Type of surgical procedure; (foot/ankle) | 17/7 |
| Duration of anaesthesia; min | 82 (75 to 137) |
| Duration of surgery; min | 49 (37 to 63) |
| Remifentanil dose; µg kg$^{-1}$ min$^{-1}$ | 0.03 (0.02 to 0.03) |
| Bispectral index | 42 (37 to 46) |
| SBP; mmHg | 97 (92 to 104) |
| Heart rate; min$^{-1}$ | 64 (56 to 73) |

Data are median (IQR, interquartile range) or number. ASA, American Society of Anesthesiologists; Ce, effect-site concentration.
measure the autonomic nervous system reactivity to a standardised noxious stimulation in non-verbal patients. For example, the sensory level following caudal anaesthesia was successfully estimated by pupillary reflex dilation measurements in children during general anaesthesia. Pupillometry unambiguously distinguished between noxious and non-noxious procedures in deeply sedated critically ill patients. In the immediate postoperative period, pupillary reflex dilation response to a standardised noxious stimulus correlated with verbal pain ratings before and after morphine titration, which suggests its potential use for patients who cannot accurately convey pain intensity in this setting.

Tetanic stimulation is considered a more predictable source of painful stimulus than other noxious procedures, such as skin incision and tracheal intubation. By incorporating a tetanic stimulator with the pupillometer we were able to accurately record a 13-s time course of pupil diameter changes to a standardised painful stimulus. The 5-s duration of the tetanic stimulus is in accordance with previous investigations on pupillary reflex dilation. This duration is long enough to produce pupil diameter effects, yet below that required to induce pain-related heart rate variability (30 s). In the present study, no changes in blood pressure and heart rate were found. Conversely, the maximum amplitude of pupil diameter was reached before completion of tetanic stimulation (see Figs 1 and 3). This suggests that pupillary reflex dilation might be mediated by the activation of nociceptors served by fast conducting Aδ-nerve fibres, as shown previously. Of note was the use of a new stimulation site to assess pupillary reflex dilation (the skin innervated by lateral sural cutaneous nerve), and our results indicated that this site was appropriate to explore pain response during general anaesthesia.

As expected, we found pupillary reflex dilation amplitudes of only 15 to 20% in response to stimulation of the untreated territory, much less than the 50 to 200% changes in pupil size reported in earlier studies. During combined epidural and general anaesthesia, pupil dilation response to tetanic stimulation exceeded 50% in the non-blocked segment. As mentioned earlier, no or only very low doses of opioids were concomitantly administered in these studies. In anaesthetised children subjected to skin incision, the addition of low-dose alfentanil (10 μg kg⁻¹) markedly dampened the pupillary reflex dilation response. A negative linear relationship between pupil dilation response and predicted remifentanil concentration was found with a 50% reduction in the maximal pupil dilation response at a theoretical concentration of 2.3 ng ml⁻¹. With simulated remifentanil concentrations of less than 2.3 ng ml⁻¹ for all patients, our data concerning noxious stimulation of the non-blocked leg confirm the close dependency of pupil size measurements upon the administration of opioids.

With a continuous infusion of remifentanil, we did, however, also note that pupillary reflex dilation responses to tetanic stimulation could be further reduced and even blunted for most patients following sensory blockade. Blockade efficiency was confirmed postoperatively with all assessed patients reporting no cold sensation in the popliteal region of the sciatic nerve territory. Concordant with data obtained in patients given epidural anaesthesia with no concomitant opioids, our findings show that an additional substantial dampening of pupillary reflex dilation is achieved when the peripheral sensory nerve block is associated with continuous infusion of remifentanil. Of note was the consistent additional decrease in pupillary reflex dilation measurements associated with stimulation of the blocked leg (see Fig. 2), suggesting...
that the technique has enough sensitivity to detect such an additional change in noxious transmission.

There are some limitations to our study. First, our aim was to find differences in the pupillary reflex dilation response to stimulation of non-blocked and blocked nerve territories under general anaesthesia. To determine whether pupillary reflex dilation magnitude could be related to the efficacy of regional block in anaesthetised patients would require the gradual increase in intensity of tetanic stimulation. In addition, whether this technique might be useful in guiding intraoperative administration of opioids remains to be explored. Second, the study of pupillary reflex dilation response without concomitant opioid would have been of particular value. However, this study was observational and did not interfere with the protocol of anaesthesia routinely used for such patients. Third, the quality of the sensory block was not assessed prior to induction of general anaesthesia and we were not able to exclude patients with an unsuccessful block from the pupillary reflex dilation measurements. Finally, electrical stimulation was applied to, and evaluation of post-operative block was performed on, the area of skin innervated by the lateral sural cutaneous nerve, a sensitive branch of the common fibular nerve. The assessment of tibial nerve block would have required theplantar placement of stimulation skin electrodes. The popliteal sciatic nerve block was performed with ultrasound guidance to visualise the spread of the local anaesthetic around both the tibial and common fibular nerves, thus making an incomplete tibial nerve block unlikely.

Conclusion
In conclusion, pupillary reflex dilation monitoring combined with tetanic stimulation was used as an indicator of peripheral nerve block efficacy during propofol–remifentanil anaesthesia. We found marked differences in pupillary reflex dilation measurements according to whether the stimulated leg was under unilateral popliteal sciatic nerve blockade or normal conditions, even during continuous infusion of remifentanil. These results are a proof of concept, and pupillometry appears to be a sensitive tool to measure autonomic nervous system reactivity during general anaesthesia.

Acknowledgements
Assistance with the study; the authors wish to thank Thierry Bagnol, (engineer, IDMed, Marseille), for his technical help, and Professor Hervé Bouaziz (Department of Anaesthesia, University of Nancy, Nancy, France) for his helpful discussion regarding the study. They also thank Professor Philippe Merloz (Department of Orthopedics, Grenoble University Hospital, Grenoble, France), and Drs Emmanuel Briot, Pascal Incagnoli, Léon N’Kashama and Bashar Oummahan (Department of Anaesthesia and Critical Care, Grenoble University Hospital, Grenoble, France) for their assistance with the study.

Financial support and sponsorship: provided solely from departmental sources.

Conflict of interests: none declared.

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