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Abstract

Background

Pain intensity is usually self-rated by patients with a numeric rating (NRS) scale but this scale cannot be used for non-communicating patients. In anesthetized patients, experimental noxious stimulus increases pupillary diameter (PD) and pupillary light reflex amplitude (PLRA), the difference between PD before and after light stimulation. Labor pain is an intense acute non-experimental stimulus, effectively relieved by epidural analgesia. The goals of this prospective observational study were therefore to describe the effects of labor pain and pain relief with epidural analgesia on PD and PLRA, to determine their association with pain intensity and to determine the ability of a single measurement of PD or PLRA to assess pain.

Methods

In a first stage, pain (11-point NRS), PD, and PLRA were measured in 4 conditions in 26 laboring women: before and after epidural analgesia and in the presence and absence of a uterine contraction. Pupillometry values among the 4 conditions were compared and the strength of the association between absolute values of pain and PD or PLRA and between pain and changes in PD or PLRA brought about by uterine contraction assessed with r^2 . In a second stage, one measurement was performed in 104 laboring women. Strength of the association between pain and PD or PLRA was assessed with r^2 . The ability of PD or PLRA to discriminate pain (NRS>4) was also assessed.

Results

In the first stage, a statistically significant increase in pain, PD and PLRA was observed during a contraction and this change was abolished after epidural analgesia. The r^2 for the association between pain and changes in PD (r^2 =0.25, 95%CI [0.07;0.46]) or PLRA (r^2 =0.34 [0.14;0.56]) brought about by a uterine contraction was higher than the r^2 for the association between pain and absolute values of PD (r^2 =0.14 [0.04;0.28]) or PLRA (r^2 =0.22 [0.10;0.37]) suggesting a stronger association for changes than for absolute values. In the second stage, r^2 was 0.23 [0.10;0.38] for PD and 0.26 [0.11;0.40] for PLRA and the area under the receiver operating characteristics curve was 0.82 [0.73;0.91] and 0.80 [0.71;0.89], respectively.

Conclusions

Changes in PD and PLRA brought about by a uterine contraction may be used as a tool to assess analgesia in non-communicating patients.

MESH Keywords Adolescent ; Adult ; Analgesia, Epidural ; Analgesia, Obstetrical ; Female ; Humans ; Labor Pain ; diagnosis ; Pain Management ; Pain Measurement ; methods ; Pregnancy ; Prospective Studies ; Reflex, Pupillary ; drug effects ; Young Adult

Author Keywords Analgesia ; Epidural ; Labor ; Obstetric ; Reflex ; Pupillary

Introduction

Evaluation of acute pain intensity and pain relief with analgesic techniques usually relies on patients' self-rating with visual analog or numeric rating scales (NRS) (1–3). These scales are of no help in patients with impaired consciousness who are frequently encountered during the postoperative period or in patients with communication barriers, a growing issue for healthcare providers in western multicultural and multilingual societies (4). Behavioral pain scales have been developed for non-verbal patients, such as ICU patients (5). Unfortunately, no behavioral acute pain scale has been specifically developed for adult surgical patients. Additionally, ethnic or cultural

differences may compromise the use of such a scale (6). Thus, an objective tool to measure acute pain intensity or the effectiveness of analgesia would be of benefit to both patients and healthcare providers.

Increase in pupillary diameter (PD) is observed after application of an experimental noxious stimulus in anesthetized or sedated ICU patients (7,8). This pupillary dilation reflex to pain is attenuated by intravenous opioids or inhaled nitrous oxide (9–12). It has therefore been proposed during general anesthesia as a tool to guide opioids administration. Similarly, pupillary light reflex amplitude (PLRA), the difference between PD before and after light exposure, increases after application of an experimental noxious stimulus in patients under general anesthesia (7,11,13). However, to the best of our knowledge, no study has examined the effect of a natural, non-experimental, noxious stimulus in conscious patients on PD and PLRA. Labor pain is an intense, non-experimental, noxious stimulus that can be effectively relieved with lumbar epidural analgesia. Investigating the effects of labor pain and pain relief with epidural analgesia on PD and PLRA may therefore be a first step to evaluate pupillometry as a tool to assess acute spontaneous pain intensity and pain relief with analgesic techniques in conscious patients. Moreover, it could be helpful for the caregiver to determine in conscious patients if a single pupillometry assessment can discriminate patients with pain from patients without pain in order to start an analgesic intervention rather than monitor the effect of an analgesic intervention with repeated pupillometry assessments.

The goal of the first stage of this two-stage observational study was, firstly, to describe the effects of labor pain and pain relief with epidural analgesia on PD and PLRA, and, secondly, to study the association between pain and PD or PLRA. The goal of the second stage was to determine the ability of a single measurement of PD or PLRA to discriminate laboring women with and without pain.

Methods

This study was approved by the local Institutional Review Board of Hotel-Dieu Hospital (“Comité pour la Protection des Personnes, Ile de France 1”), Assistance Publique-Hôpitaux de Paris, France. Informed written consent was obtained from each patient. The study took place in the Delivery Unit of Bichat Hospital, an academic hospital with 2200 deliveries per year and an 87% epidural analgesia rate.

Study design

This was a 2-stage clinical study assessing laboring women in four conditions: no epidural analgesia, no uterine contraction (NoE/NoC); no epidural analgesia, during a uterine contraction (NoE/C); with epidural analgesia, no uterine contraction (E/NoC); with epidural analgesia, during a uterine contraction (E/C). Non-inclusion criteria were contraindication to epidural analgesia, patient's refusal to participate, ocular disease, diabetes, hypertension or preeclampsia.

In the first stage, a convenience sample of 25 women in labor were planned to be included. Pupillary and pain assessments were performed 4 times in each patient, before and after initiation of epidural analgesia, in the following order: NoE/NoC, NoE/C, E/NoC, and E/C. Each woman was used as her own control and two paired samples were defined for each patient. The first paired sample was before epidural analgesia with two conditions (contraction or no contraction) and the second paired sample was after epidural analgesia with two conditions (contraction or no contraction).

In the second stage, inclusion of 100 laboring women was planned, with 25 patients in each of the four following conditions: NoE/NoC, NoE/C, E/NoC, and E/C. Once the number of patients in the first condition was obtained (NoE/NoC), patients in the second condition (NoE/C) were recruited and so on. Pupillary and pain assessment was performed once in each patient.

Lumbar epidural analgesia technique

Epidural analgesia was initiated at the request of the patient without regard to stage of labor or cervical dilation at the time of the request. The procedure was performed in the sitting position using a midline approach and loss-of-resistance to saline technique. Five minutes after a test dose of 2 mL of lidocaine 20 mg/mL without epinephrine, 5 μg of sufentanil and 5 mL of ropivacaine 1 mg/mL were injected through the epidural catheter. Ten minutes after the test dose, a second bolus of 5 mL of ropivacaine 1 mg/mL was administered. Thirty minutes after the test dose, patient-controlled epidural analgesia (ropivacaine 1 mg/mL with sufentanil 0.25 μg/mL) was initiated (patient bolus: 5 mL, lockout interval: 10 minutes, basal infusion rate: 1 to 5 mL/h, maximum volume: 30 mL/h).

Pupillary assessment

Pupillary assessment was performed with an infrared portable dynamic videopupillometer (Neurolight®, IDMed Company, Marseilles, France) (14). One assessment consisted in a 5-second video recording of pupillary diameter with a sampling frequency of 67 Hertz (i.e. a pupillary diameter recorded every 15 milliseconds). During the 5-second video recording, flashlight stimulation was applied to elicit the pupillary light reflex and the pupillary diameter before and after the flashlight calculated. Flashlight illumination was 320 Lux and luminance was 1280 Candela/m^2 .

Pupillary diameter (PD) before the flashlight stimulation was obtained during the interval beginning 0.4 seconds before the flashlight and ending with the flashlight (i.e. a 400 milliseconds interval with 27 pupillary diameters recorded). PD before the flashlight was defined as the median of the 6 highest pupillary diameters among the 27 diameters recorded during this interval. PD after the flashlight was obtained during the interval beginning 0.3 seconds after the flashlight and ending 1.3 seconds after the flashlight (i.e. a 1000 milliseconds interval with 67 pupillary diameters recorded). PD after the flashlight was defined as the median of the 6 lowest pupillary diameters among the 67 diameters recorded during this interval. PLRA was calculated as the difference between PD before the flashlight and PD after the flashlight stimulation. Retinal illuminance (i.e. the measure of light stimulus that drives the pupil into contraction) was calculated as luminance multiplied by pupil area before the flashlight.

To avoid the influence of ambient lighting in the room on pupillary light reflex, the pupillometer included a preformed silicone membrane surrounding the orbit under investigation. During the recording, patients stayed in a half-sitting position, with the eyes under investigation looking straight ahead. A video recording was performed as follows: the pupillometer was applied to the orbit, then the patient was asked to close the contralateral eye and the recording started. When the patient was not able to close the contralateral eye during the pupil scan, it was closed by the investigator by applying a gentle downward traction on the superior eyelid. Blinking during pupil scan was detected by the visual inspection of the recording; these recordings were discarded and the recording repeated.

One 5-second pupillary assessment was performed in once in each of the four conditions (NoE/NoC, NoE/C, E/NoC, and E/C). The recording during a contraction started at the beginning of the increase in intrauterine pressure identified on an external tocodynamometer. The recording with epidural analgesia was performed at least 30 minutes after the test dose.

Pain assessment

At the completion of pupil scan, pain intensity was assessed by the patient with an 11-point numeric rating scale (zero: “no pain”, ten: “ the worst imaginable pain”) (2,3). A value greater than 4 defined pain.

Statistical analysis

The results are presented as number of patients (%), or mean ± SD and (range). When appropriate, 95% confidence intervals [95%CI] were calculated. Statistical analyses used the R software, version 2.14.1 (R Foundation for Statistical Computing, Vienna, Austria). A p-value < 0.05 was considered significant.

To compare pain, PD, or PLRA among the 4 conditions, we first performed an analysis of covariance with a global test for the difference among conditions taking repetition within patients into account. If this global test was significant, we performed three paired t-tests to compare NoE/C vs NoE/NoC, E/NoC vs NoE/NoC and E/C vs E/NoC, with p-values adjusted with the Holm correction. An adjusted p-value < 0.05 was considered significant. Each analysis of covariance was also completed by an analysis including the baseline value of pain, PD, or PLRA, respectively, as a covariate to test the influence of baseline. Moreover, for PLRA, an analysis of covariance including retinal illuminance as a covariate was also performed to determine if PLRA values were related to retinal illuminance changes resulting from pupil size area changes.

The relationship between pain (NRS) and absolute values of PD was assessed with a linear mixed-effects model, since repeated measurements within patient (i.e. the four conditions) were analyzed. We assumed uncorrelated additive error and a normally distributed patient intercept random effect. A similar analysis was performed for PLRA. We also used a linear mixed-effects model to study the relationship between NRS and changes in PD brought about by a uterine contraction (C minus NoC) in the two conditions (E or NoE). A similar analysis was performed for PLRA. Performance of each model was assessed with the Bayesian information criterion (BIC). A lower value of the BIC indicates a better model performance and a difference of BIC greater than 10 between two models suggests very strongly that the model with the lower BIC is better (15). Strength of the association was assessed with the specific r^2 for mixed-effects models, the square of the correlation coefficient r between the observed and fitted values of pain in the model, and its 95% confidence interval (16). This value indicates the proportion of the variation of pain accounted for by the linear mixed-effects model.

In the second stage, inclusion of 100 patients was based on an expected correlation coefficient r of 0.35 between PLRA and NRS. To obtain a power of 90% with a type I error of 5%, at least 82 patients had to be included (i.e. at least 20 patients per group). The association between pain (NRS) and PD or PLRA in the four independent groups of patients combined (NoE/NoC, NoE/C, E/NoC, and E/C) was assessed with linear regression and the strength of the association with the coefficient of determination r^2 . The ability of PD or PLRA to discriminate patients with and without pain (NRS>4 and NRS≤4, respectively) was assessed with the area under the ROC curve (AUC) (1). Comparison of the AUC used the DeLong method. The 95% confidence interval of the difference between the two AUC was calculated with bootstrap resampling (b=2000) and the percentiles method.

Results

Twenty-six patients were included in the first stage and 104 patients in the second stage. Their characteristics are presented in Table 1. No patient complained of having a light flashed into her eyes.

First stage

Pain (NRS), PD, and PLRA measurements in the 4 conditions (NoE/NoC, NoE/C, E/NoC, and E/C) are summarized in Figure 1. ANCOVA demonstrated a significant difference for pain, PD, and PLRA ($p < 0.0001$ for pain, PD and PLRA). ANCOVA results were unchanged when incorporating baseline values of pain, PD, or PLRA. The difference for PLRA remained significant in the analysis of covariance including retinal illuminance as a covariate ($p = 0.002$).

In the first paired sample before epidural analgesia, a significant increase in pain (mean difference 7.3, 95%CI [7.2; 8.5]), in PD (+ 14 % [10; 18]) and in PLRA (+ 43% [31; 55]) was observed during a uterine contraction when compared with no uterine contraction. In the second paired sample after epidural analgesia, a small but significant increase in pain during uterine contraction was observed when compared with no uterine contraction (mean difference 1.5 [1.0; 2.3]). One patient had a NRS > 4 during the contraction. However, no significant changes in PD and PLRA were observed during auterine contraction when compared with no uterine contraction.

In the absence of contraction, a statistically significant decrease in pain (mean difference −0.5 [−0.6; −0.1]) was observed after epidural analgesia when compared with before epidural analgesia. No patient in the absence of contraction had a NRS value greater than 4. A similar decrease in PD (− 10% [−15; −4]) but not in PLRA (− 5% [−16; 6]) was observed.

Graphical displays of the relationships between the 104 absolute values (all the conditions combined) of pain and PD or PLRA are presented in the upper panel of Figure 2. A significant relationship between pain and PD and between pain and PLRA was observed with linear mixed-effects models ($p = 0.0001$ and $p < 0.0001$, respectively). Values for r^2 were 0.14 [0.04; 0.28] for PD and 0.22 [0.10; 0.37] for PLRA. The BIC was 554 for PD and 542 for PLRA.

Graphical displays of the relationships between pain and the 52 changes in PD or PLRA (C minus NoC) in the 2 paired samples are presented in the lower panel of Figure 2. A significant relationship between pain and PD changes and between pain and PLRA changes was observed with linear mixed-effects models ($p = 0.0004$ and $p < 0.0001$, respectively). The values for r^2 were 0.25 [0.07; 0.46] for PD changes and 0.34 [0.14; 0.56] for PLRA changes. The BIC was 278 for PD and 272 for PLRA.

Second stage

Pain (NRS), PD and PLRA measurements in the four groups of the validation stage are presented in Table 2. A significant relationship between pain and PD ($p < 0.0001$) and between pain and PLRA ($p < 0.0001$) was observed with linear regression (Figure 3). Values for r^2 were 0.23 [0.10; 0.38] for PD and 0.26 [0.11; 0.40] for PLRA. The AUC of the ROC curve discriminating patients with NRS>4 from patients with NRS ≤ 4 was 0.82 [0.73; 0.91] for PD and 0.80 [0.71; 0.89] for PLRA with no statistically significant difference between the 2 AUC ($p=0.39$). The difference between the two AUC was 0.02 [−0.02; 0.07].

Discussion

Increase in PD and PLRA after application of an experimental noxious stimulus has been thoroughly investigated in anesthetized patients but less is known in non-anesthetized ones (7–11,13). In conscious healthy volunteers, Ellermeier et al. and Höfle et al. reported that pupillary dilation occurs after application of pressure on the fingers and Oka et al. that this response is attenuated by analgesic agents such as inhaled nitrous oxide (12,17,18). Similarly, Aissou et al. observed a pupillary dilation in postoperative patients after application of a standardized noxious stimulus close to skin incision that was attenuated by intravenous morphine titration (14). However, to our knowledge, no study has examined, the effect of a natural noxious stimulus such as labor pain on PD and PLRA in conscious patients, and determined if pupillometry could be used as a tool to assess pain in this population.

Our study showed that, similar to surgical or experimental pain, a significant increase in PD and PLRA was observed during uterine contraction in the first paired sample before epidural analgesia. The increase in pain, PD and PLRA during uterine contraction were abolished in the second paired sample after epidural analgesia. Since changes in PD and PLRA paralleled changes in pain, we hypothesized that pain associated with labor and pain relief with epidural analgesia were responsible for pupillometry measurements changes. However, increase in retinal illuminance resulting from pupillary dilation during uterine contraction may have been responsible for the observed increase in PLRA. The analysis of covariance taking retinal illuminance into account ruled out this hypothesis. The relationship between pain and pupillary measurements was further confirmed by the association between pain and absolute values of PD or PLRA or between pain and changes in PD or PLRA brought about by a uterine contraction in the two paired samples. These results are similar to those in previous studies in anesthetized patients which demonstrated an attenuation of the dilation of the pupil or of the pupillary light reflex amplitude in response to an experimental noxious stimulus with analgesia (9–11,19). These changes constitute the rationale supporting the use of pupillometry to guide opioid administration during general anesthesia.

The higher correlation coefficient for changes as compared to absolute values suggests that the association between pain and changes in PD or PLRA was stronger than the association between pain and absolute values of PD or PLRA. It also suggests that repeated pupillometry measurements to evaluate pain changes after an analgesic intervention may be more appropriate than a single pupillometry measurement to diagnose pain and decide an analgesic intervention.

In the absence of uterine contraction, a significant decrease in PD and a statistically significant but not clinically relevant decrease in pain were observed after epidural analgesia when compared with before epidural analgesia. We suggest that a direct effect of epidural opioids on pupil size is responsible for this decrease in PD, similar to the myosis induced by intravenous morphine in conscious patients without noxious stimulus (20,21). A direct effect of local anesthetic on pupil diameter is unlikely since it was demonstrated that intravenous administration of lidocaine to reach a plasma concentration of 5 μg/mL has no effect on pupillary diameter (22). The absence of decrease in PLRA may be explained by the decrease in both PD before the flashlight and PD after the flashlight, since PLRA is the difference between PD before and after the flashlight. We decided not to use a control group of patients without epidural sufentanil administration to specifically assess the effects of opioids on pupillary measurements because the use of sufentanil is our routine practice.

In the second stage, a weak association between absolute values of pain and PD or PLRA was observed. The ability of PD and PLRA to discriminate patients with and without pain had an AUC of 0.82 and 0.80, respectively (23). This does not support our initial hypothesis that a single pupillometry assessment could identify patients with pain and help decide an analgesic intervention. It reinforces the suggestion that repeated pupillometry measurements may help monitor pain changes after an analgesic intervention and underlines the need for complementary studies.

It should be noted that all statistical analyses performed assumed normal distribution of the variables, which is unlikely for NRS because of the number of zero values. However, the statistical modeling was mainly exploratory and did not intend to make strong inferences. The 95%CI of r^2 also relies on this assumption and should be evaluated cautiously. Anyhow, the statistical methods used are rather robust with respect to departure from normality assumption.

Use of numeric rating scale to assess pain intensity is limited by communication skills of the patients. These scales are of no help in case of impaired consciousness that is frequently encountered during the postoperative period or in case of communication barriers such as language barrier (4). We have studied a very specific group of patients, women in labor, and they are not representative of all conscious patients experiencing pain. The results may therefore not be similar in other types of acute non-experimental pain such as acute postoperative pain. This highlights the need for complementary studies. However, in our opinion, this study provides a clinical evaluation for a tool that may be used to monitor the balance of nociception/analgesia in other situations with poorly communicating or non-communicating patients such as sedated critically ill patients or drowsy patients in the postanesthesia care unit.

Bias may have resulted from the fact that the same investigator performed pupil scans and recorded patient's pain. However, evaluation of pupil size by the investigator is an objective measurement provided by the videopupillometer and the investigator only recorded self-rated pain by the patient which did not require investigator interpretation. Moreover, pupil scans were made before measuring pain in order to minimize the bias resulting from knowledge of the status of the disease (i.e. pain or no pain) (24).

In conclusion, changes in PD and PLRA are associated with pain brought about by a uterine contraction. These assessments may be a useful tool to monitor pain after an analgesic intervention in non-communicating patients. Further studies are required to confirm this suggestion and determine its utility in other types of acute non-experimental pain.

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Figure 1

Boxplots of pain (NRS, 11-point scale), pupillary diameter (PD) and pupillary light reflex amplitude (PLRA) in the two paired samples (before epidural analgesia (NoE) and after epidural analgesia (E)) with two conditions (no uterine contraction (NoC) and during a uterine contraction (C)) in the 26 patients of the first stage. The thick horizontal line indicates the median, the limits of the box the 25th and 75th percentiles and the whiskers the interquartile range.

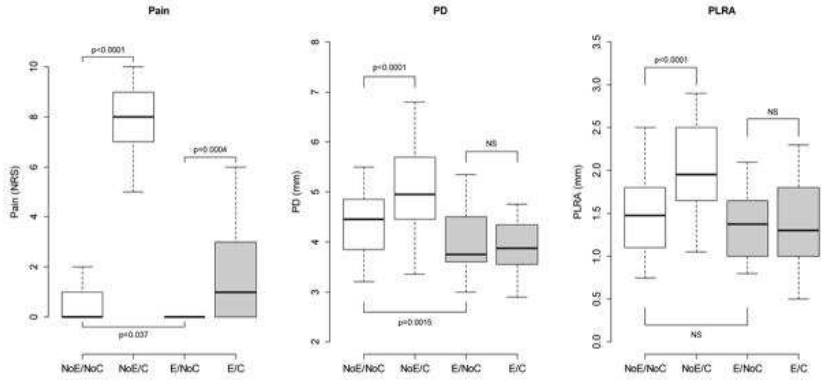

Figure 2

Upper panel: Relationship between pain (NRS) and the 104 absolute values of pupillary diameter (PD) (left panel) or pupillary light reflex amplitude (PLRA) (right panel) in the first stage (4 conditions combined). The thick black line represents the regression line obtained from the linear mixed-effects model. r^2 [95% confidence interval] indicates the proportion of the variation of pain accounted for by the model.

Lower panel: Relationship between pain during uterine contraction and the 52 variations (C minus NoC) of PD (left panel) or PLRA (right panel) in the two paired samples in the first stage. The red points represent patients without epidural (NoE) and the grey points the patients with epidural (E). The thick black line represents the regression line obtained from the linear mixed-effects model.

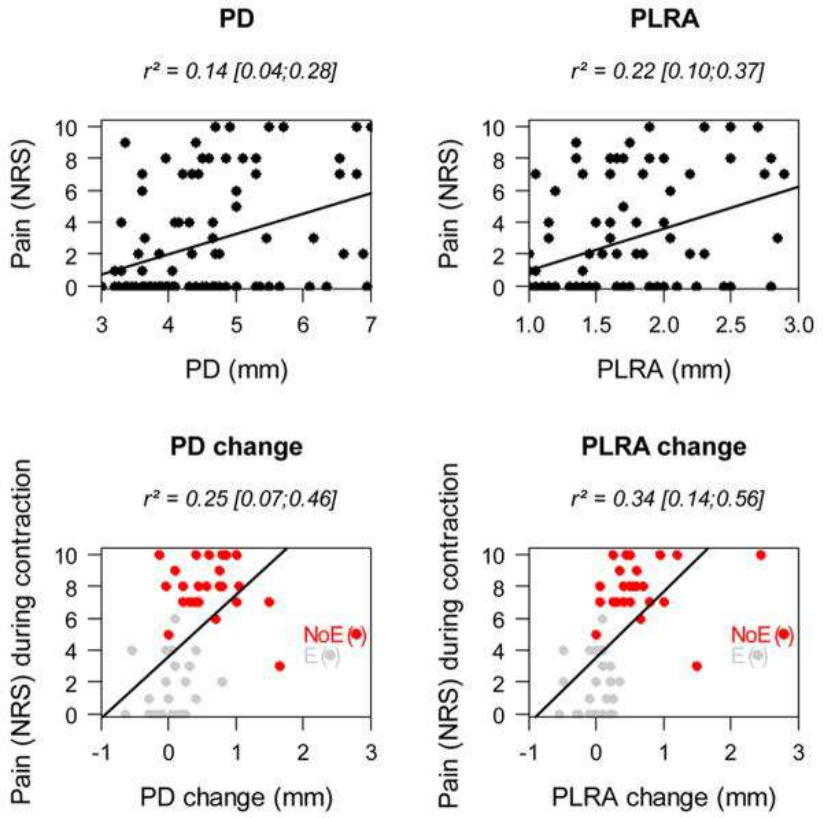

Figure 3

Relationship between pain (NRS), pupillary diameter (PD) (left panel) or pupillary light reflex amplitude (PLRA) (right panel) in the 104 patients of the second stage. The thick black line represents the regression line obtained from the linear regression. r^2 [95% confidence interval] indicates the proportion of the variation of pain accounted for by the model

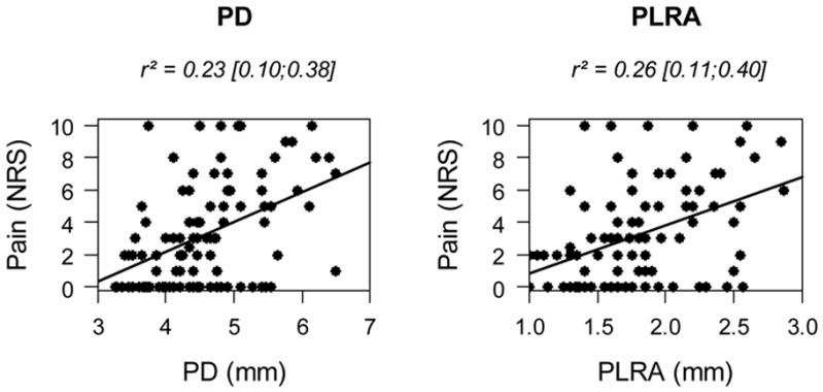

Table 1

Characteristics of the patients in the first and second stages.

	First stage n = 26	Second stage n = 104
Age (years)	32 ± 5 (23; 41)	30 ± 5 (18; 41)
Body mass index at term (kg/m^2)	29.2 ± 4 (22.3; 37.3)	28.2 ± 4 (21.3; 44.9)
Parity including current pregnancy		
Primiparous	13 (50%)	66 (63%)
Multiparous	13 (50%)	38 (36%)

Results are expressed as mean ± 1 standard deviation and (range) or number of patients (%).

Table 2

Pain (NRS), pupillary diameter (PD), and pupillary light reflex amplitude (PLRA) in the second stage.

	NoE/NoC n = 26	NoE/C n = 27	E/NoC n = 25	E/C n = 26
Pain (NRS)	0.9±1.3 (0;4)	7.4±1.9 (4;10)	1.0±1.4 (0;5)	2.9±1.8 (0;7)
NRS > 4	0 (0%)	26 (96%)	1 (4%)	5 (19%)
PD (mm)	4.3±0.9 (2.7;6.5)	5.2±0.8 (3.7;6.5)	4.2±0.6 (3.2;5.5)	4.3±0.5 (3.4;5.4)
PLRA (mm)	1.6±0.6 (0.5;2.6)	2.2±0.5 (1.3;3.5)	1.6±0.4 (0.9;2.4)	1.7±0.3 (1.0;2.5)

Results are expressed as mean ± 1 standard deviation and (range) or number of patients (%)

NoE/NoC: no epidural analgesia, no uterine contraction; NoE/C: no epidural analgesia, during uterine contraction; E/NoC: epidural analgesia, no uterine contraction; E/C: epidural analgesia, during uterine contraction.