Diagnostic Capability of Pupillary Dilation Reflex to Measure Pain In The Critical Analgosedated Patient

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Abstract

Background: Pain continues to be an underdiagnosed problem. Objective tools are needed for its assessment. The objective of this study was to determine the diagnostic performance, validity and reliability of the pupillary dilation reflex (PDR) against the Behavioural Pain Scale (BPS) to assess pain in patients under light-moderate sedation.

Methods: A study of diagnostic tests using PDR versus BPS as a reference test was performed. The patients were recruited from the Intensive Care Units of the Araba University Hospital and were consecutively admitted. They were older than 18 years, under intravenous analgosedation, mechanically ventilated and had a BPS score of three and a Richmond Agitation and Sedation Scale (RASS) score between -1 and -4. The responses to a non-painful (NP) stimulus, 10 mA, 20 mA, 30 mA and 40 mA stimuli, and was assessed with the BPS and PDR. PDR measurements were performed with an Algican® pupilometer. Pain was considered to be present at BPS≥4. The receiver operating curve (ROC) was plotted, and the area under the curve (AUC) was calculated. We identified the cut-off points showing the highest sensitivity and specificity. Diagnostic performance was studied based on the Youden index, negative predictive value (NPV), positive predictive value (PPV), accuracy, positive likelihood ratio (PLR), and negative likelihood ratio (NPC) of each of them. They are presented with their 95% confidence intervals (CI).

Results: Thirty-one patients were included and 183 measurements were performed. 49 (27%) measurements showed a painful response according to the BPS. We obtained an AUC of 0.885 (95% CI 0.830-0.940). The PDR value with the best diagnostic efficacy was 11.5%, which had a sensitivity of 89.8% (95% CI 78.2-95.6) and a specificity of 78.4% (95% CI 70.6-84.5) with an accuracy of 81.4 (75.2-86.4). The agreement between BPS and PDR had a kappa index of 0.6.

Conclusions: Pupillometry could be a valid alternative for identifying pain in analgosedated critical patients.

Trial registration

Phase 1 of the project PUPIPAIN ClinicalTrials.gov Identifier: NCT04078113

Background

Pain is a notable problem in critical patients that is usually related to both the clinical situation and the use of invasive procedures during admission, and it often exceeds the effect of prescribed analgesics [1]. The incidence of pain in intensive care units (ICUs) can reach 70% [2, 3]; it persists in 40% of patients 1 year after discharge from the ICU, and it comprises the most unpleasant lasting memory of the time in the ICU [4, 5]. Inadequate pain management triggers anxiety [6, 7], hyperadrenergic symptoms, sleep disruption [5], posttraumatic stress syndrome [8] and chronic pain [9–11]. In contrast, excessive sensitization to pain can lead to the overuse of sedatives and analgesics, which leads to the appearance

of ileus and hypoactive delirium and the subsequent prolongation of mechanical ventilation times and ICU stays [12, 13].

Pain monitoring with behavioural scales is recommended [10, 14–16]. Behavioural scales have shown adequate psychometric properties for the detection of pain in analgosedated patients; however, their validity depends on the level of sedation, the patient's pathology and/or severity and the subjective judgement of the person administering the scale [14, 16–18]. A valid and reproducible measure of pain is required to allow safe and standardized clinical practices.

Currently, the performance of tools that measure the responses of the autonomic nervous system to nociceptive stimulation as an indicator of pain in surgical patients is being studied [19–25]. Such tools are non-invasive devices based on the cardiac sympathetic response. However, this parameter is also easily distorted by the patient's haemodynamic situation, the use of inotropic drugs or the appearance of arrhythmias. Therefore, the results may not be applicable to patients admitted to the ICU.

The pupillary dilation reflex (PDR), an autonomous physiological response to nociception, could be an objective indicator of the presence of pain in sedated critical patients. Infrared video pupillometry is a non-invasive, innocuous technique that accurately measures the pupillary reflex after nociceptive stimulation and detects changes in pain situations [26–30]. It has allowed the assessment of different levels of nerve block in regional anaesthesia [31, 32] and the management of opioid use [33, 34] during surgery. There are two studies in which pupillometry has obtained very interesting results in critical patients [29, 30], although the subjects were limited to deeply sedated patients and probably do not reflect current analgosedation patterns.

In the last decade, there has been a change in the management of analgosedation. The recommended use of more superficial levels of sedation and the growing need for more accurate pain assessments were factors that determined the performance of this study. We assessed pain in patients with light-moderate sedation and determined the validity and reliability of pupillometry with respect to the Behavioural Pain Scale (BPS).

Methods

It was a prospective study of diagnostic tests, that assessed the diagnostic capability of pupillometry, to discriminate pain by comparing the behaviour of the PDR with the BPS scale as a reference method. A study protocol was prepared, and the data from the study are available in a private repository of Osakidetza Basque Health System.

Patients

Patients older than 18 years who were admitted to the ICU of the Araba University Hospital, analgosedated and on mechanical ventilation, unable to communicate verbally and had a baseline BPS score of three and a RASS score between − 1 and − 4 were included. Those who presented limitations in

the behavioural expression of pain (e.g., due to treatment with muscle relaxants, neuromuscular diseases with motor impairment or severe polyneuropathy) and those with ophthalmic pathologies with pupillary involvement, involvement of the third cranial nerve, Glasgow scores < 6, intracranial hypertension and the use of atropine, clonidine, dexmedetomidine, tramadol, ketamine, adrenaline, calcium antagonists and antiemetics were excluded.

Patients who met the eligibility criteria were selected consecutively during the first week of admission to the unit. Consent for the participation of relatives and/or legal representatives were obtained. A sufficient number of subjects were included until at least 50 measurements with pain response according to BPS were reached.

Study protocol

A single protocol was performed with each patient, during which pre-stimulus baseline measurements were taken and the maximum post-stimulus variations were recorded. The patient's responses were recorded at different pain levels: non-painful (NP) stimulus, calibrated electrical stimulations with increasing intensities of 10 mA, 20 mA, 30 mA and 40 mA and endotracheal aspiration (ETA). As NP stimulus, we slided a gauze pad over an uninjured area of the patient's forearm. ETA is a commonly performed procedure in the ICU that is considered among the most painful daily interventions that a patient undergoes [1–3]. Prior to the protocol, the patients remained at rest and did not undergo potentially painful interventions for at least 1 hour. Alarms were silenced to avoid possible interference with the pupillary response. An interval of 5 minutes was maintained between stimulations until the initial pupil size was recovered. The analgesia and sedation regimen remained constant throughout the protocol. The patients showed a baseline pain level on the BPS equal to 3.

Pupillary measurements were performed with a Neurolight AlgiScan® portable video pupillometer (ID Company, Marseilles, France). The pupillometer has a video camera with infrared light, which allows measurements to be performed in the dark without interfering with the pupillary response and in response to both light and calibrated electrical stimuli. It has a measurement range between 0.1 and 10 mm (pupil size), with an accuracy of 0.1 mm and a resolution of 0.01 mm, maintaining an image acquisition and measurement frequency of 62 Hz. It measures the basal pupil diameter prior to stimulation and the maximum pupil diameter, and it calculates the percentage of pupil size variation with the formula (Var. = (Max-Min.)/Min.*100). The assessment of the variation in pupil size during NP and ETA stimulation was performed in DPR mode and was maintained for 20 seconds. Calibrated stimulations were delivered through an electrode placed on the ulnar nerve, on the inside of the wrist, and on clean skin free of any lesion. Pupil size was measured with the pupillometer in Tetanus mode at an optimal impedance level identified by the pupillometer. The measurements started 2–3 seconds after the placement of the pupillometer on the eye to allow the pupil to adapt to the dark environment generated by the silicone eye protector.

Pain was assessed using the validated BPS [17, 35–37]. Scores equal to or greater than 4 points were considered indicative of pain.

A team of two researchers took the measurements simultaneously and independently during the procedure: a researcher in charge of the PDR measurements and the researcher who collected the BPS. The nurse in charge of the patient performed the NP and the ETA (Fig. 1).

Statistical analysis

The sample size was calculated following the method proposed by Flahault et al. [38]. With a predicted test sensitivity of 0.95 and a (95%) confidence limit not lower than 0.80, the need for approximately 50 cases with pain was identified.

A descriptive study of the baseline clinical and demographic characteristics of the participants was performed using means and deviations, medians and interquartile ranges for continuous variables, and numbers and percentages for qualitative variables. A study of diagnostic tests using PDR versus BPS as a reference test was performed. The receiver operating curve (ROC) was plotted, and the area under the curve (AUC) was calculated. We identified the cut-off points showing the highest sensitivity and specificity. Diagnostic performance was studied based on the Youden index, negative predictive value (NPV), positive predictive value (PPV), accuracy, positive likelihood ratio (PLR), and negative likelihood ratio (NPC) of each of them. They are presented with their 95% confidence intervals (CI). Finally, the reliability of the pupillometry was assessed by calculating the degree of agreement between the tools and the kappa index.

All complete data from both diagnostic tests (PDR and BPS) were analysed.

Statistical calculation was performed with the statistical programme IBM SPSS Statistics version 23.0. The level of significance was set at $p < 0.05$.

Results

Between May 1, 2017, and May 31, 2018, 31 patients were recruited from the Intensive Care Unit (ICU) of the Araba University Hospital (Fig. 2). Both medical and surgical patients were included. 61.3% of the sample were men, and the mean age of the sample was 62.9 ± 17.1 years. The mean Bispectral index (BIS) score was 63 ± 19.46, and the mean RASS was − 3.39 ± 0.76. All patients were receiving continuous intravenous analgesic treatment. The baseline pain level of the included patients with BPS was three. The general characteristics of the sample and the distribution of drugs and analgesics used are shown in Table 1.

Table 1
General characteristics of the patients (n = 31)

Age (yr) mean (SD)	**62.9 ± 17.1**
Sex ratio male/female, n (%)	19/12 (61.3/38.7)
Body mass index (kg/m^2), median (25-75th percentile)	27 (24–30)
Acute Physiology And Chronic Health Evaluation II, median (25-75th percentile)	21 (16.5–23.5)
Bispectral index (BIS), mean (SD)	63 ± 19.46
RASS, mean (SD)	-3.39 ± 0.76
Admission	
Acute respiratory failure n (%)	8 (25.8)
Postoperative n (%)	10 (32.2)
Sepsis n (%)	9 (29.1)
Multiple trauma n (%)	4 (12.9)
Sedative, analgesic and vasoactive drugs during the procedure	
Propofol, n (%)	9 (29.03)
Dose, (mg/kg/h) mean (SD)	1.49 ± 0.88
Midazolam, n (%)	16 (51.6)
Dose (mg/kg/h), mean (SD)	0.09 ± 0.05
Fentanyl, n (%)	20 (64.5)
Dose (µg/kg/h), mean (SD)	1.14 ± 0.74
Remifentanil, n (%)	8 (25.8)
Dose (µg/kg/h), mean (SD)	7.05 ± 4.12
Morfina, n (%)	3 (9.6)
Dose (mg/kg/h), mean (SD)	1.00 ± 0.44
Norepinephrine, n (%)	22 (71)
Dose (µg/kg/min), mean (SD	0.2 ± 0.13
Dobutamine, n (%)	3 (9.7)
Dose (µg/kg/min), mean (SD)	4.10 ± 0.97

183 measurements were performed; 134 yielded BPS scores < 4, and 49 yielded BPS scores ≥ 4. There were 3 missing data and no indeterminate index test or reference standard results. All measurements

were performed correctly with both instruments (BPS and PDR), and observed simultaneously. Researchers who were also members of the intensive care unit's team of professionals performed BPS measurements. The BPS scale was a standard tool in the unit, included in the unit's pain management protocol. PDR measurements were performed in strict accordance with the manufacturer's recommendations. No adverse effects were recorded during the use of either diagnostic tool.

Primary outcome

The ROC curve corresponding to the sensitivity and specificity values for each PDR percentage value with respect to the BPS is presented. The AUC was 0.885 (95% CI, 0.830–0.940) (Fig. 3). PDR values of 11.5%, 7.5%, 5.5% and 3.5% were identified as possible cut-off points for the assessment of pain. The sensitivity of the selected points was close to 90%. Cut-off points of 11.5% presented precision and Youden index values of 0.8 and 0.7, respectively and had the highest specificity, with 78.4% (95% CI, 70.6–84.5). This point also registered the highest PPV of 60.3%, with a 95% CI of 48.8–70.7. The NPVs were close to 95% for all cut-off points. The rest of the diagnostic parameters were also more favourable for the PDR cut-off point of 11.5% than for 7.5%, 5.5% and 3.5% (Table 2).

Table 2
Diagnostic capability of different PDR cut-off points (global measurements = 183)

	PDR 11.5%	PDR 7.5%	PDR 5.5%	PDR 3.5%
Sensitivity (%)	89.8 (78.2–95.6)	89.8 (78.2–95.6)	93.9 (83.5–97.9)	95.9 (86.3–98.9)
Specificity (%)	78.4 (70.6–84.5)	62.7 (54.3–70.4)	51.5 (43.1–59.8)	38.1 (30.3–46.5)
PPV (%)	60.3 (48.8–70.7)	46.8 (37.0-56.8)	41.4 (32.7–50.7)	36.2 (28.4–44.7)
NPV (%)	95.5 (89.8–98.0)	94.4 (87.5–97.6)	95.8 (88.5–98.6)	96.2 (87.2–99.0)
FP (%)	21.6 (15.5–29.4)	37.3 (29.6–45.7)	48.5 (40.2–56.9)	61.9 (53.5–69.7)
FN (%)	10.2 (4.4–21.8)	10.2 (4.4–21.8)	6.1 (2.1–16.5)	4.1 (1.1–13.7)
Accuracy (%)	81.4 (75.2–86.4)	69.9 (62.9–76.1)	62.8 (55.6–69.5)	53.6 (46.3–60.6)
PLR	4.15 (2.9–5.8)	2.4 (1.9–3.06)	1.94 (1.6–2.3)	1.6 (1.4–1.8)
NLR	0.13 (0.06–0.3)	0.16 (0.07–0.36)	0.12 (0.04–0.36)	0.1 (0-0.4)
Youden´s Index	0.7	0.5	0.5	0.3

Date are shown as a percentage with a 95% confidence interval (CI); PPV: positive predictive value; NPV: negative predictive value; FP: false positives; FN: false negatives; PLR: positive likelihood ratio; NLR: negative likelihood ratio.

Secondary outcomes

Pupillometry showed 82.4% agreement with the BPS scale and a kappa index of 0.6 ($p = 0.001$). In 15.8% of cases, the behavioural scale did not reflect pain (BPS < 4), but pain was detected by the PDR (PDR >

11.5%). Only 2.7% of the discrepancies occurred in situations in which the BPS registered pain, but the PDR did not (Table 3).

Table 3
Agreement between BPS and PDR

Stimulus	Total agreement BPS/PDR	Disagreement BPS < 4/PDR ≥ 11.5	Disagreement BPS ≥ 4/PDR < 11.5	Coefficient of agreement (Kappa)
	n (%)	n (%)	n (%)	k (p)
NP	29 (93.5)	2 (6.5)	–	–
10mA	29 (93.5)	2 (6.5)	–	–
20mA	24 (77.5)	7 (22.6)	–	0.29 (0.022)
30mA	25 (80.7)	3 (9.7)	3 (9.7)	0.56 (0.002)
40mA	18 (64.3)	8 (28.6)	2 (7.1)	0.3 (0.077)
ETA	24 (77.4)	7 (22.6)	–	–
Global measurements	149 (82.4)	29 (15.8)	5 (2.7)	0.6 (0.0001)

Data are presented as number of patients (n) and percentage (%).k: Kappa index; NP: non-painful; ETA: endotracheal aspiration

Discussion

The obtained parameters qualify the PDR as a test with good diagnostic performance in relation to BPS and suggest that it is potentially useful for the identification of pain in critical patients under light-moderate sedation. A PDR cut-off of 11.5% was able to determine the presence of pain in patients, with a Youden index of 0.7 and a sensitivity and specificity of 90% and 80%, respectively.

The detection of pain in critical patients requires new indicators that provide more information about their nociceptive response to stimuli. The gold standard for assessing pain is self-referential scales, which are not an option for sedated patients and those on mechanical ventilation. In these cases, although the use of behavioural scales is recommended, behavioural responses may be distorted in critical patients and may not adequately reflect the presence of pain [39]. The PDR is an objective measure of nociception that has shown good results in different groups of patients. Aissou et al. [33], working with a group of 100 conscious patients during the immediate postoperative period, obtained a PDR cut-off point of 23% with sensitivity, specificity, PPV and NPV greater than 90%. Sabourdin et al. [40] observed a PDR higher than 32% in a group of surgical patients who showed behavioural changes after continuous nociceptive stimulation between 5 and 60 mA. This cut-off point obtained an AUC of 0.758 and a sensitivity and specificity of 0.65 and 0.77, respectively. In critical patients, two pioneering studies have analysed

pupillary reactivity in pain situations. First, Lukaszewicz et al. [30] assessed the pupillary response to a light stimulus and concluded that a variation greater than 23% could be an indicator of pain. Second, Paulus et al. [29] used calibrated nociceptive stimuli lower than 40 mA and observed an increase in PDR as the intensity of the stimuli increased and a greater response in patients who presented pain according to a behavioural scale; thus, they proposed the use of pupillometry as a tool for predicting the presence of pain during ETA. Both PDR and the behavioural scale showed the pupillary reactivity in deeply sedated critical patients (RASS-5), but the PDR showed optimal diagnostic performance, with sensitivity and specificity greater than 80% and an NPV above 90%.

The PDR results obtained for our group of patients under light-moderate sedation indicated that pupillometry had a good diagnostic performance similar to that reported in the consulted studies of patients under deep sedation. Our PDR threshold of 11.5% showed the ability to diagnose the presence of pain, with a PLR and NLR of 4.15 (2.9–5.8) and 0.13 (0.06–0.3), respectively; these data supported its possible diagnostic utility for both detecting pain and ruling out its presence. The PDR, in turn, showed 82.45% agreement with the BPS and a kappa index value of 0.6. Our study is one of the few published papers to analyse the reliability of PDR versus BPS for detecting pain. The agreement in the group of patients who showed pain on the BPS was greater than 97%. On the other hand, the PDR was higher than 11.5% in up to 15% of patients who did not exhibit pain on the BPS. That is, the PDR detected nociception according to our pain threshold in patients classified as pain-free according to the baseline behavioural scale.

However, we must keep in mind that the PDR is a reflex that represents an autonomous alerting response and could be influenced by other types of stimuli that are perceived as harmful. Therefore, the protocol was performed in a controlled clinical environment. To minimize the influence of these factors on the measurements, intense light or auditory stimuli that could generate pupillary responses unrelated to the response to pain were avoided. Similarly, a window of 1 hour with no other procedures (mobilizations, placement of central venous catheters, removal of devices and wound healing) was established prior to the measurements to ensure that the measurements reflected only the response to stimuli administered during the protocol.

A possible limitation of this study was the use of behavioural pain scales as a reference tool for assessing the presence of pain in patients. The subjective nature of behavioural scales and the limited behavioural expression of pain in some patients make the diagnosis of pain in critical patients difficult, which may condition therapeutic decisions. Based on our results, the discriminative capacity of the behavioural scale for detecting pain could have been compromised in some patients. The behavioural responses observed were sometimes minimal, leading us to question the suitability of behavioural scales for this purpose.

Pain assessment and treatment strategies have evolved rapidly in recent years through the incorporation of goal-directed pain management protocols [10, 16, 41, 42]. However, the degree of implementation of these protocols is highly variable [43, 44]. The subjective nature of the scales hinders agreement among

professionals. Pupillometry is a tool that allows accurate measurements of changes in pupil size in response to nociceptive stimuli. It is an easy technique to implement and to include in routine clinical practice since it shows data clearly and instantaneously.

Conclusions

The measurement of PDR allowed the detection of nociceptive responses to different stimuli in analgosedated patients and showed adequate validity and reliability compared with the BPS scale. The PDR demonstrated the ability to detect pain with a high degree of agreement with the BPS scale. We believe that pupillometry could allow the objective monitoring of pain in critical patients, thus facilitating the effective and individualized management of analgesia. New studies that analyse the clinical impact of our results are recommended.

Abbreviations

AUC
Area under the curve
BIS
Índice Biespectral
BMI
Body mass index
BPS
Behavioural Pain Scale
C
Consent
CI
Confidence intervals
ETA
Endotracheal aspiration
Hz
Hertz
ICU
Intensive care unit
M
measurements
mA
Milliampere
Max
Maximum
Min

Minimum
MD
Mean difference
mm
Millimetre
NP
Non-painful
NPC
Negative likelihood ratio
NPV
Negative predictive value
PDR
Pupillary dilation reflex
PLR
Positive likelihood ratio
PPV
Positive predictive value
RASS
Richmond Agitation and Sedation Scale
SD
Standard deviation
Var
Variation

Declarations

Ethics approval

The Clinical Research Ethics Committee of Basque Country approved this study.

Consent to participate

Informed consent was obtained from all individual participants included in the study or their legally authorized representatives.

Consent for publication

All authors approved the final manuscript.

Availability of data and material

The data from the study are available in a private repository of Osakidetza Basque Health System.

Conflicts of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Authors' contributions

YL, AV, and NP carried out the conception and design of the study, material preparation, and analysis. YL, AV, NA, AQ, CR, PP, ZG, AM and LA contributed to data collection. The first draft of the manuscript was written by YL. AV, NP and AQ commented on earlier versions of the manuscript. All authors read and approved the final manuscript.

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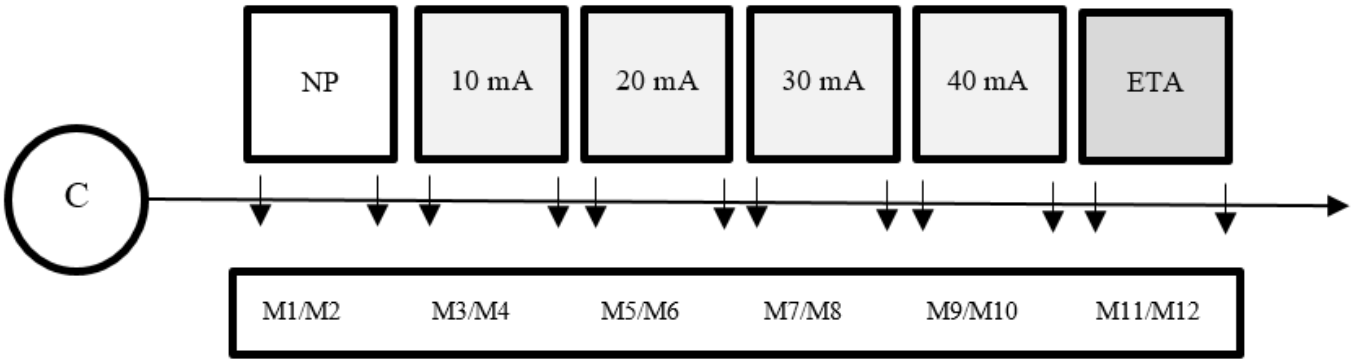
Figures



C: Consent; M: Measurement (BPS/PDR); NP: Non painful estimulus; mA: Miliamperes; ETA: Endotracheal aspiration; 5 minutes was maintained between stimulations

Figure 1

Study design

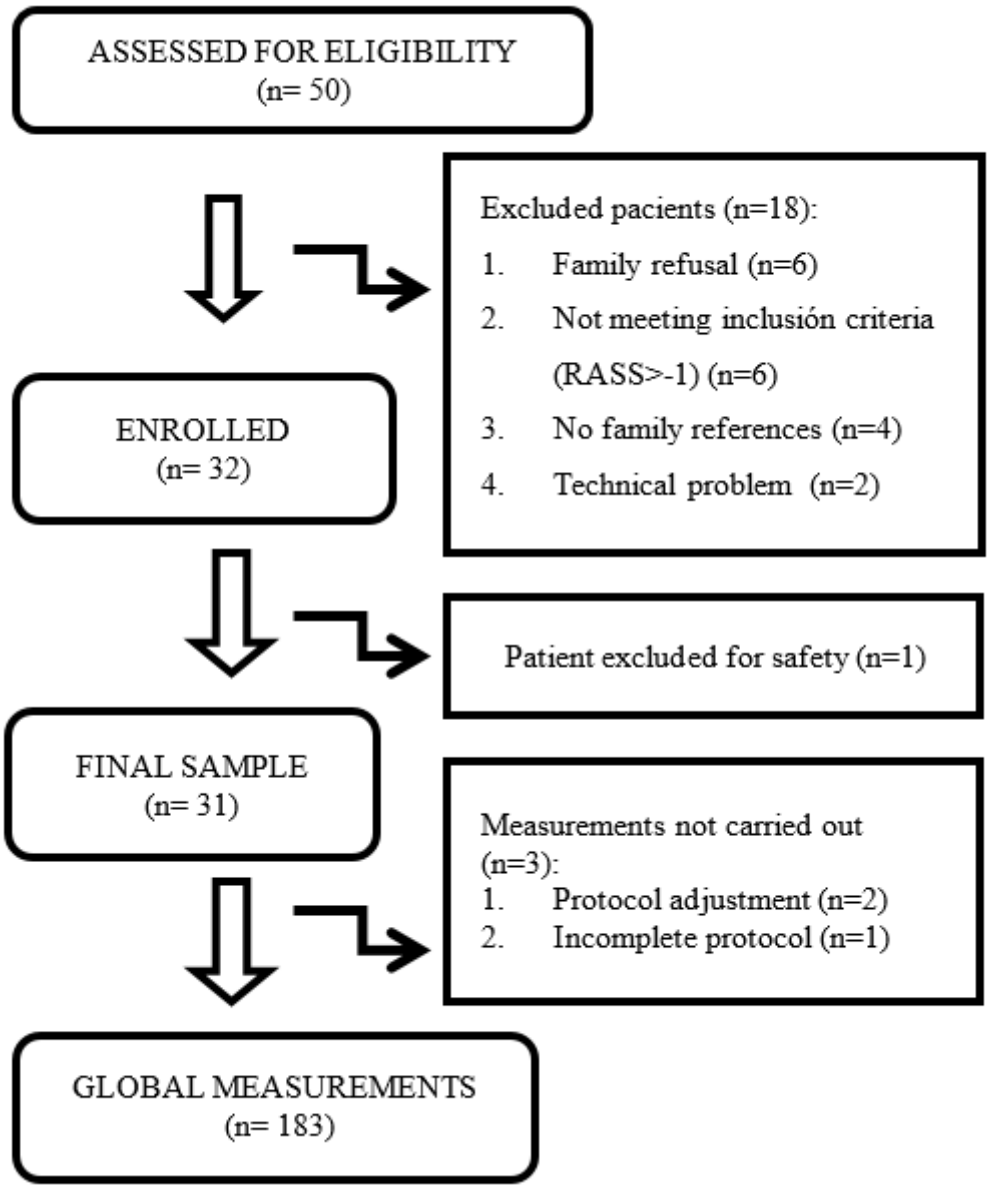


Figure 2

Flowchart of recruited patients

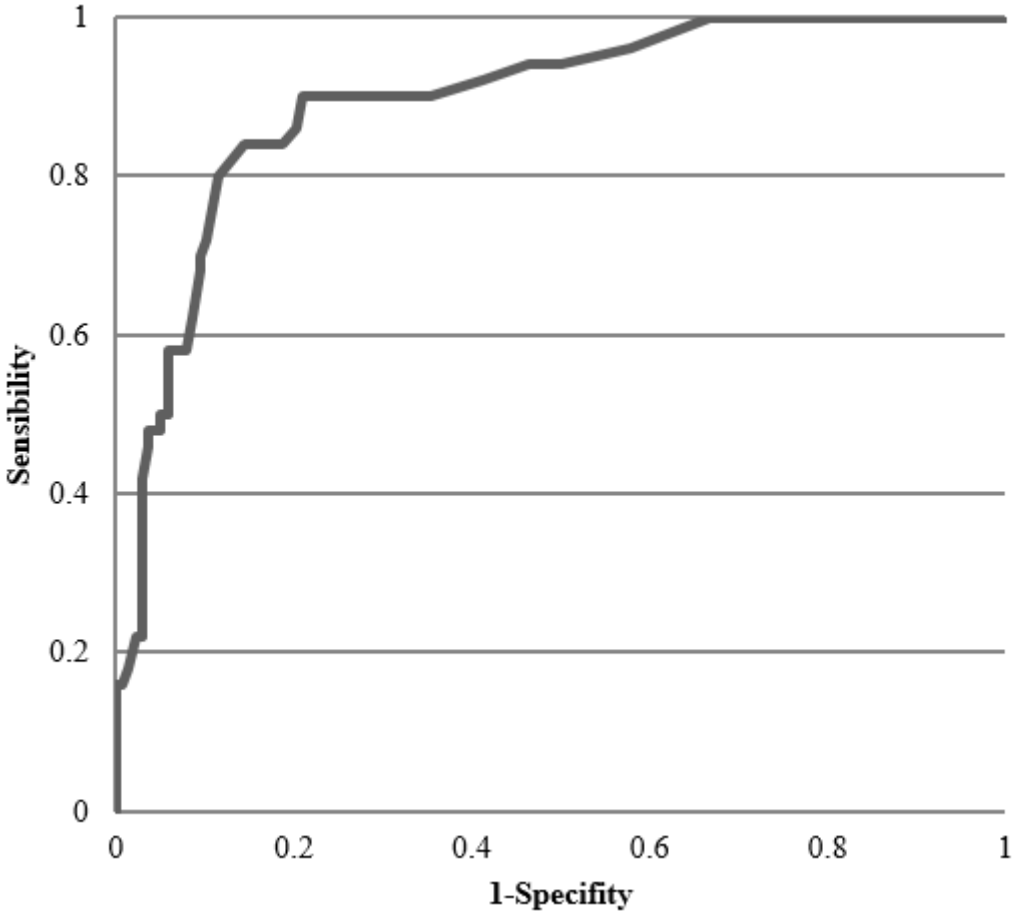


Figure 3

Area under the indicative curve of pain according to PDR

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- STARD2015Checklist1.docx