NICE advice

NPi-200 for pupillary light reflex in critical care patients

Medtech innovation briefing
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Summary

- The **technology** described in this briefing is NPi-200. It is used to measure pupillary light reflex and pupil diameter in patients in critical care.
- The **innovative aspects** are that the neurological pupil index, a proprietary index developed from more than 600,000 normative data sets, allows pupil reactivity and other parameters to be trended over time, like other vital signs.
- The intended **place in therapy** would be as an alternative to manually checking pupillary response using a pen torch in critical care units.
- The **main points from the evidence** summarised in this briefing are from 6 observational studies including a total of 1,217 people in critical care units. They show that NPi-200 can measure additional parameters compared with standard care and predict poor outcomes in people who are critically ill.

- **Key uncertainties** around the evidence or technology are that only 1 comparative observational study was included, which did not report on patient outcomes and none of the studies were conducted in the UK.
- The **cost** of NPi-200 is £17.50 per patient, per 7-day stay in a critical care unit, with hourly observations (excluding VAT). The **resource impact** would be greater than standard care, which is around £1.50 for a pen torch.

The technology

NPi-200 (Neuroptics) is a handheld automated pupillometer that includes a camera and a colour touch screen. It provides precise, accurate and objective measurements of pupil size and pupillary light reflex (PLR), as well as other parameters including minimal pupil diameter, percentage change in pupil size and constriction velocity, and displays a video of the constriction response. Measurement takes around 3 seconds per eye. The NPi-200 is used with a disposable SmartGuard. The SmartGuard positions the NPi-200 at a consistent distance to perform the scan. SmartGuard is a single-patient-use device with smart-card technology that can store patient data for each patient for the length of their admission. The SmartGuard has an radio-frequency identification memory tag that can store up to 168 paired pupil measurements, which can be uploaded to the person's electronic medical record or downloaded to a computer for research purposes.

The SmartGuard reader is required for integrating the data into electronic medical records. A barcode scanner is available to avoid manual input of patient data.

Innovations

The company claims that, unlike manual PLR assessment, the NPi-200 expresses PLR in a numerical readout using the 'neurological pupil index' (NPi). The NPi is a proprietary index that is a numerical expression of the PLR on a scale from 0 to 4.9, where an NPi of 3 or higher is considered a healthy response. NPi was validated based on data from over 600,000 people with normal pupillary light reflexes. This allows an objective measurement to be taken so that, like other vital signs, changes from baseline can be recorded over time. The company also claims that a reduction in NPi of more than 0.7 can be used to predict neurological deterioration several hours before a person develops symptoms. A difference in NPi of 0.7 or more between pupils may be considered abnormal (anisocoria). The company claims that the early warning has a substantial unquantifiable benefit

because it allows people to be treated earlier.

Current care pathway

Pupillary reactions are usually checked manually using a pen torch, which can lead to inter- and intra-observer variability. Pupil size is recorded in millimetres (1 mm to 9 mm) before light stimulus. Size charts are available, often printed on the side of the pen torch. To assess the PLR, the ambient light is dimmed and the person is asked to fixate on a distant target. The right eye is illuminated from the right side and the left from the left side. Direct pupillary response (the pupil constricts when the light is shone on to it) and a consensual response (the other pupil also constricts) is noted. Pupil size is measured, ideally with reference to a neurological observation chart. PLR is subjectively classed as brisk, sluggish or non-reactive.

A clinical expert said that it is often difficult to adequately dim the ambient light in the intensive therapy unit and people who are critically ill are usually unable to comply with requests to fixate on a distant target. Pen torch assessments are performed regularly by nurses as part of routine neurological assessments, and intermittently by junior doctors to confirm findings. Minimal training is required to use the pen torch, but experience is essential to accurately judge the speed of pupillary response and presence or absence of anisocoria.

The following publications have been identified as relevant to this care pathway:

- NICE's COVID-19 rapid guideline on managing COVID-19
- NICE's guideline on suspected neurological conditions: recognition and referral
- NICE's guideline on rehabilitation after critical illness in adults
- NICE's guideline on acutely ill adults in hospital: recognising and responding to deterioration.

Population, setting and intended user

NPi-200 is indicated for use in the clinical management of children and adults in critical care, specifically in neuro critical care, cardiac critical care, paediatric critical care and stroke units. The company states that it is important to establish a baseline reading as

soon as possible for all critically ill people and that people at risk of neurological decline should be continually monitored.

The technology is used by clinicians and intensivists, in relevant tertiary settings. Because of their learned experiences across multiple disciplines, the technology is now becoming nurse-led in many locations.

The company states that the device is simple to use and requires minimal training. Key aspects of the training involve understanding and using the available data. Training is tailored to the users and can be one-to-one or group training, and can be provided face-to-face or online via Microsoft Teams. Training for key users for each commission is included in the purchase price. Training videos and materials are available.

Costs

Technology costs

The NPi-200 consists of 2 components, the NeurOptics NPi-200 automated pupillometer and the NeurOptics NPi-200 'SmartGuard'. The SmartGuard reader is necessary to integrate the data into the electronic medical record. The barcode scanner avoids the need for manual input of patient data.

- NeurOptics NPi-200 automated pupillometer: £4,155
- NeurOptics NPi-200 SmartGuard: £396 for 24
- Barcode scanner and charging cradle by socket: £475 to £595
- SmartGuard reader: £150 to £195.

The company states that the NeurOptics NPi-200 automated pupillometer has an initial cost of about £4,000, which over a 5-year period with a cohort of 800 patients per year amounts to £1.00 per patient. The NeurOptics NPi-200 SmartGuard costs £16.50 per device. Each SmartGuard has an inbuilt radio-frequency identification chip that stores up to 168 paired measurements, which is enough for hourly pupil examinations over a typical 7-day stay in critical care (336 data sets per £16.50 or £0.049 per data set). The total cost of the NeurOptics NPi-200 and SmartGuard per patient for a 7-day stay in a critical care unit is therefore £17.50, or £2.50 per day.

Costs of standard care

Pupillary reactions are usually taken manually using a pen torch. One expert said that a pen torch costs approximately £1.50 and that most staff purchase their own.

Resource consequences

The company states that the technology is currently used in 28 NHS trusts.

The company claims that the use of the automated pupillometry can save valuable nursing time.

The raw data obtained from the automated pupillometer can be included in patient notes and changes tracked over time like other vital signs.

Regulatory information

NPi-200 is a CE-marked class I medical device.

The following manufacturer field safety notices or medical device alerts for this technology have been identified:

NeurOptics NPi-200, MAUDE report number 6913426, September 2017. It was reported that the charger docking station had a design error, with the charger burning out within 60 days of operation. This was resolved in January 2018.

The Medicines and Healthcare products Regulatory Agency said that the complaint seems to be from a single device user and does not have an associated recall or other field safety corrective action from the manufacturer. The affected component is the power supply, which is likely to be different in the UK and therefore has limited relevance to the UK market.

Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Older people and people with poor health or pre-existing conditions are more likely to be admitted to critical care units. NPi-200 is intended for use in critically ill people. Age and disability are protected characteristics under the Equality Act (2010).

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with NICE's interim process and methods statement for the production of medtech innovation briefings. This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

Published evidence

There are 6 studies summarised in this briefing, including a total of 1,217 people.

All studies are observational, with 2 being multicentre studies and most studies investigating the prognostic value of the NPi-200. There are further studies that are not summarised here.

The clinical evidence and its strengths and limitations is summarised in the overall assessment of the evidence.

Overall assessment of the evidence

The evidence for the technology is of low methodological quality, and most of the studies are small in terms of patient numbers. For 2 of the studies it was unclear in which country the study took place, and none of the studies were done in the UK. Only 2 studies had a comparator, however they did not report on patient outcomes. The studies show that NPi-200 can predict poor outcomes in critically ill people. Further evidence comparing NPi-200 with standard care, with a large sample size is needed.

Robba et al. (2019)

Study size, design and location

A single-centre prospective observational study of 112 critically ill people.

Intervention and comparator(s)

Neurolight Algiscan (NL) and NPi-200 compared with standard pupillary light reflex (PLR).

Key outcomes

There was a significant correlation between the 2 automated pupillometry devices for pupil size, constriction to light stimulation and constriction velocity, but not for pupillary latency. The NL and the NPi-200 devices' mean bias for pupil size was -0.12 mm (limit of agreement [LoA] -1.29 mm to 1.06 mm), for pupil constriction -1.0% (LoA -9.3% to 7.2%), and for latency 0.02 ms (LoA 0.22 ms to 0.25 ms). There was a significant correlation between pupil size evaluated by clinical examination and by the NL or NPi-200 devices. The mean biases for pupil size measured using NL and NPi-200 and clinical examination were 0.16 mm (LoA -0.99 mm to 1.32 mm) and 0.21 mm (LoA 3.03 mm to 3.30 mm), respectively. Although there was significant correlation between NL and NPi-200 values and clinical examination of the PLR, the 2 devices were not always interchangeable, especially for the evaluation of pupillary latency.

Strengths and limitations

This study compares 2 automated pupillary devices to each other and to standard care (pen torch). The devices were used in random order. This study did not assess the effect of automated pupillary findings on patient outcomes. Furthermore, neurological pupil index (NPi) was not assessed as this was not available in both devices. It is unclear in which country the study took place.

Miroz et al. (2019)

Study size, design and location

A prognostic observational cohort study in Switzerland of 100 people who had been

sedated and were undergoing mechanically ventilated venoarterial extracorporeal membrane oxygenation (VA-ECMO) therapy.

Intervention and comparator(s)

NPi-200 pupillometer.

Key outcomes

Non-survivors (n=57) had significantly lower NPi than survivors at all time points (all p<0.01). Abnormal NPi (less than 3, at any time from 24 hours to 72 hours) was 100% specific for 90-day mortality, with no false positives. Adding the 12-hour PREDICT VA-ECMO score to the NPi provided the best prognostic performance (specificity 100%, 95% confidence interval [CI] 92 to 100; sensitivity 60%, 95% CI 46 to 72; area under the receiver operating characteristic curve [AUC] 0.82). Quantitative NPi alone had excellent predictive ability for poor outcome from day 1 after VA-ECMO insertion, with no false positives. Combining NPi and 12-hour PREDICT VA-ECMO score increased the sensitivity of outcome prediction, while maintaining 100% specificity.

Strengths and limitations

This is the first clinical study testing the role of automated pupillometry as a neuromonitoring tool for the early prediction of outcome in people receiving VA-ECMO. One of the authors is consultant to and a member of the scientific advisory board of NeurOptics.

Riker et al. (2019)

Study size, design and location

A prospective diagnostic accuracy study of 55 adults given targeted temperature management after initial cardiac arrest.

Intervention and comparator(s)

NPi-200 pupillometer.

Key outcomes

All 9 people with 1 or more non-reactive pupil (NPi=0) within 6 hours (range 2 hours) after recovery of spontaneous circulation (ROSC) died, and 86% (12 of 14) with sluggish pupils (NPi less than 3) had poor outcomes. Out of 29 people with normal pupil reactivity (NPi of 3 or more), 15 (52%) had poor outcomes. During targeted temperature management, 95% (20 of 21) of people with non-reactive pupils had poor outcomes, 64% (9 of 14) of people with sluggish pupils had poor outcomes, and 45% (9 of 20) of people with normal pupil reactivity had poor outcomes. Pupil size did not predict outcome, but NPi (AUC 0.72 [0.59 to 0.86]; p<0.001), PLR constriction percentage (AUC 0.75 [0.62 to 0.88]; p<0.001) and constriction velocity (AUC 0.78 [0.66 to 0.91]; p<0.001) at 6 hours predicted poor outcome. The best predictor of poor outcome in the first 6 hours after ROSC was an NPi less than 3.7. Very early after resuscitation from cardiac arrest, abnormal NPi and PLR measurements by pupillometer are predictive of poor outcome and are not usually associated with dilated pupils.

Strengths and limitations

It is possible that some results may present false positives. A convenience sample was taken. It is unclear in which country the study took place.

Oddo et al. (2018)

Study size, design and location

A prospective observational multicentre study of 456 comatose adults at day 1 and day 2 after cardiac arrest, in 10 European countries.

Intervention and comparator(s)

NPi-200 pupillometer compared with standard manual PLR (sPLR).

Key outcomes

Between day 1 and 3, an NPi of 2 or less had a 51% (95% CI 49 to 53) negative predictive value (NPV) and a 100% positive predictive value (PPV; 0% false-positive rate, 95% CI 0 to 2), with a 100% (95% CI 98 to 100) specificity and 32% (95% CI 27 to 38) sensitivity for the prediction of unfavourable outcome. Using the cut-off of abnormal NPi (less than 3)

increased sensitivity (38%, 95% CI 32 to 44) but at the expense of a lower specificity (96%, 95% CI 92 to 98; 6% false-positive rate). Compared with NPi, sPLR had significantly lower PPV and significantly lower specificity (p<0.001 at day 1 and day 2; p=0.06 at day 3). The combination of NPi of 2 or less with bilaterally absent somatosensory evoked potentials (SSEP; n=188 patients) provided higher sensitivity (58% [95% CI 49 to 67] compared with 48% [95% CI 39 to 57] for SSEP alone), with comparable specificity (100% [95% CI 94 to 100]).

Strengths and limitations

This study indicates that quantitative pupillometry had higher accuracy than sPLR in predicting poor outcome after cardiac arrest, with no false positives, and significantly higher specificity than standard manual pupillary examination.

Obling et al. (2019)

Study size, design and location

An observational study in Denmark of 221 resuscitated comatose people in 3 groups: out of hospital cardiac arrest (OHCA), in hospital cardiac arrest (IHCA) and other including with cardiac diagnoses.

Intervention and comparator(s)

NPi-200 pupillometer.

Key outcomes

Information about 30-day mortality was available for all people in the study. 135 people had OHCA and 51 (38%) people died within 30 days. The median NPi values were 4.10 (interquartile range [IQR] 0.60) in survivors compared to 2.80 (IQR 3.43) in people who did not survive (p<0.0001). Higher NPi values were independently associated with a lower 30-day mortality (odds ratio 0.15, 95% CI 0.06 to 0.29; p<0.0001), and the univariable model had an AUC of 0.87, with a maximal AUC cut-off level for NPi being 3.30 (sensitivity 69% and specificity 93%, PPV 85% and NPV 83%). For people with IHCA and other cardiac diagnoses, they found no association between NPi values and 30-day mortality, and the univariable models showed poor predictive values.

Strengths and limitations

This study highlights that automated infrared pupillometry is a promising prognostic tool in patients following resuscitation from OHCA.

Al-Obaidi et al. (2019)

Study size, design and location

A prospective observational multicentre replication study of 273 people (16,221 pupillary observations) in neurocritical care units in the US.

Intervention and comparator(s)

NPi-200 pupillometer.

Key outcomes

Analysis of t-test indicates statistically significant differences for all right and left mean pupilometer values, except right latency (p=0.3000) and repeated measure mixed model (p=0.0001). In people with increased intracranial pressure, mean pupilometer values for left NPi, pupil dilation, pupil size and constriction velocity were lower for both eyes compared with people with normal intracranial pressure. Values were higher in both eyes for people with increased intracranial pressure compared with normal intracranial pressure for right NPi (3.98 and 3.92 respectively; p=0.0300) and left latency (0.27 and 0.25 respectively; p<0.0001). Worsening measures of the PLR using automated pupillometry are associated with elevated intracranial pressure.

Strengths and limitations

The findings from this replication study confirm and extend those of McNett et al. (2018). The registry used in this study was partially funded by NeurOptics, the company that produced the pupillometer.

Recent and ongoing studies

- Establishing Normative Data for Pupillometer Assessments in Neuro-Intensive Care (ENDPANIC). ClinicalTrials.gov Identifier: NCT02804438. Status: recruiting. Indication: neuro-intensive care unit patients. Devices: NeurOptics NPi-200. Estimated completion date: September 2022. Country: US.
- Effects of Volatile and Intravenous Anesthetics on Pupillary Function. ClinicalTrials.gov Identifier: NCT03987529. Status: not yet recruiting. Indication: abnormal pupillary functions. Devices: NeurOptics NPi-200. Estimated completion date: February 2021. Country: South Korea.

The company states that it is aware of 2 further UK studies in development.

Expert comments

Comments on this technology were invited from relevant patient organisations and clinical experts working in the field. The comments received are individual opinions and do not represent NICE's view.

All 3 experts were familiar with and had used this technology before.

Level of innovation

All experts said that the NPi-200 is innovative compared with a pen torch. The technology is innovative because it offers an objective measure of pupil size and response and potential trends in intracranial pressure. One expert said that the metric can be compared against previous readings done by different professionals, reducing inter- and intra-observer variability. Experts were not aware of any other competing or alternative technologies available to the NHS.

Potential patient impact

All experts said that using NPi-200 provides an objective, standardised and accurate measure of pupil size and reactivity. Two experts also said that it has the potential to speed up the identification of patient deterioration and provide early intervention to neurological emergency. Experts noted that NPi-200 would be of benefit to people with

acute brain injury or neurological impairment. Another expert said that NPi-200 has the potential to improve outcomes in people with raised intracranial pressure and brain trauma. Finally, 1 expert said that the use of the NPi-200 has the potential to improve outcomes by identifying changes in a person's clinical condition that otherwise could have been missed.

One expert said that 20% of intensive treatment unit (ITU) admissions had their neurological pupil index (NPi) measurements taken at some point during their admission. Another expert noted that NPi can be used for 550 to 600 patients per annum in their intensive care unit.

Potential system impact

Two experts noted that NPi-200 will cost more than the relatively inexpensive pen torch. Two experts do not expect an impact on the number of staff, or a reduction in other equipment needed as nurses will still carry a pen torch for other reasons. One expert said that NPi-200 has the potential to reduce overall cost across the whole pathway through a potential reduction in CT scanning and a reduced length of stay. It may also lead to earlier decisions to carry out brainstem testing and potentially improve the possibility of organ donation. Two experts expect a quicker response to changes in pupil size and reactivity and reduced inter-observer variability. Early intervention in raised intracranial pressure may improve functional outcomes. One expert also said that this may lead to changes in patient management. One expert noted that the use of NPi-200 has changed clinical management in their ITU regarding the decision to perform CT scans, earlier brainstem testing, and changes in medical management such as increasing target mean arterial pressure in response to a decrease in NPi.

All experts said that a short training session of about 30 minutes is needed for staff. None of the experts were aware of any safety concerns surrounding this technology.

General comments

One expert said that they use NPi-200 regularly and that it is particularly useful for people who are unconscious or paralysed. However, it can be difficult to use in small infants who are not paralysed. Another expert said that nursing staff felt that the objective nature of the NPi-200 takes away a burden of responsibility when assessing pupils, which they know may influence patient management. Nursing staff also felt that more than 1 NPi-200 device is needed per unit.

Two experts noted that NPi-200 would be in addition to current standard care, while 1 expert said that NPi-200 has the potential to replace current standard care. No barriers to adoption have been identified by the experts, apart from 1 expert noting the cost could be an obstacle.

One expert said that NPi-200 has the potential to provide a reproducible metric that can be used to monitor depth of sedation, progression of illness or presence of raised intracranial pressure. Even though the evidence does not appear to address this, the benefits remain possible.

Two experts said that further research is needed to address the uncertainty in the evidence base, including research in children and research on intracranial pressure. One expert expressed the need for high quality randomised controlled trials to demonstrate clinically relevant benefits to support investment in the technology.

Expert commentators

The following clinicians contributed to this briefing:

- Dr Helen Turnham, consultant in paediatric critical care medicine, Oxford University Hospitals NHS Trust. Did not declare any interests.
- Dr Simon Raby, consultant in neurocritical care, Oxford University Hospitals NHS Trust. Did not declare any interests.
- Dr Anthony K Parsons, specialty lead for ICU and anaesthesia, Ashford and St. Peters NHS Foundation Trust. Did not declare any interests.

Development of this briefing

This briefing was developed by NICE. NICE's interim process and methods statement for the production of medtech innovation briefings sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

Update information

Minor changes since publication

August 2022: Costings of the Smartguard device were updated throughout.

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