# Background

Opioid prescriptions in the United States have more than tripled from 1999-2014, during which there has been a staggering increase in opioid-involved drug overdose deaths. Providers need the means to objectively monitor analgesic efficacy of treatment in patients with pain to mitigate unnecessary prescriptions.

It is well established that mu opioid receptor agonists like morphine cause miosis, an effect that does not exhibit tolerance. This suggests utility in investigating pupil size and responsiveness as pharmacokinetic measures of bioavailability. An infrared pupillometer is a device that produces a short light stimulus and subsequently measures parameters of the pupillary light reflex (PLR) including maximum and minimum pupil size (MAX, MIN), maximum constriction velocity (MCV), latency period before constriction onset (LAT), change in pupil size (DELTA), and average constriction velocity (ACV).

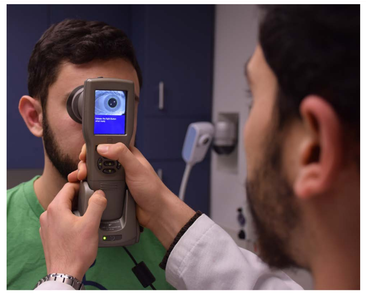

**Figure 1:** Using a pupillometer

# Purpose

The goal of this study was to use infrared pupillometry to demonstrate the pattern of changes in PLR parameters before and after receiving low dose opioid analgesia.

# Hypotheses

1. Patients receiving opioid analgesia will display differential parameters of their PLR before and after drug administration.

2. Opioid analgesics have a dose-dependent effect on parameters of the PLR.

# Methods

The Neuroptics PLR-2000 pupillometer was used to assess six pupillary parameters. Fifteen patients between the ages of 7 and 18 receiving low does opioids on patient controlled analgesia (PCA) were enrolled from the pain medicine service at Children's National Medical Center.

Patients were either post-surgical or admitted for sickle cell vaso-occlusive crisis. Baseline PLR parameters were measured prior to PCA dose. Two subsequent measurements were taken ten and fifteen minutes post PCA dose (figure 2).

**Figure 2:** Pupillary response to a light stimulus was compared before and after PCA administration

# Results

A repeated measures ANOVA was conducted to compare the effect of the opioid on specific parameters of the PLR (GraphPad Prism 7.0c). There was a significant effect of the opioid on the MAX, MIN, LAT and MCV parameters (Table 1). Dunnett's test was used to make post hoc comparisons between each parameter time point and that parameters' baseline measure. This test indicated that the 10-minute and 15-minute time points were significantly smaller than the baseline for the parameters MAX (p=.0016, p=.0010) and MIN (p=.0250, p=.0070). The LAT parameter was found to be significantly faster from baseline at the 15-minute measure (p=.0350).

Tukey's test was used to make comparisons of each time point to one another and found that there was a significant difference between the 10-minute and 15-minute time points for the MIN (p=0.0251)

| | MAX | MIN | DELTA | LAT | ACV | MCV |
|---|---|---|---|---|---|---|
| **DFn, Dfd** | 1.222, 17.11 | 1.211, 16.95 | 1.442, 20.18 | 1.882, 26.35 | 1.764, 24.70 | 1.934, 27.08 |
| **F Statistic** | 11.68 | 10.3 | 1.775 | 3.746 | 2.326 | 3.414 |
| **p-Value** | 0.0021* | 0.0036* | 0.1989 | 0.0393* | 0.1239 | 0.0490* |
| **$R^2$** | 0.4548 | 0.4239 | 0.1125 | 0.2111 | 0.7908 | 0.1961 |

**Table 1:** Repeated measures ANOVA evaluating the significance of all pupillary parameters baseline vs. post-PCA dosing.
* P-value < 0.05

# Discussion

In concordance with previous research, the MIN is significantly correlated with opioid concentration dose-dependently across the 15-minute measurement window. Current data support the efficacy of using infrared pupillometry to detect high dose opioid presence, but this research specifically demonstrates its efficacy in monitoring low dose therapeutic levels.

Establishing the pupillometer as a pharmacokinetic analog has many clinical applications. For example, genetic testing for polymorphisms that play a role in opioid metabolism (ex CYP2D6, OPRM1) can be eliminated. More widespread applications include the continuous monitoring of patients' opioid response to minimize unnecessary administration and to identify tolerance and hyperalgesia.

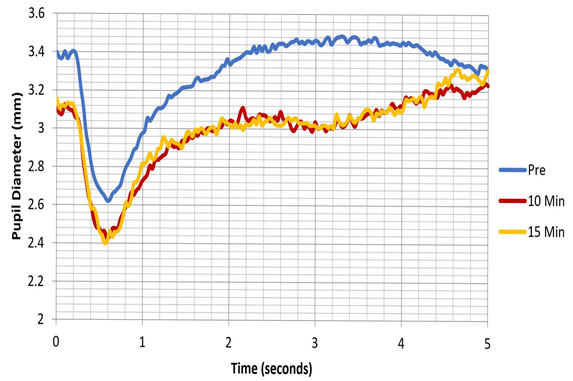


**Figure 3:** PLR of an individual patient on PCA opioid pain control. Time points show the opioid induced decrease in pupil diameter and change in pupil response.

# Next Steps

- Compare PLR parameters to blood levels of opioid metabolites to further support the efficacy of this novel pharmacokinetic measure
- Create an algorithm combining PLR data with pharmacodynamics--subjective pain scores-- to determine opioid sensitivity, tolerance, and hyperalgesia.
- Develop a noninvasive tool to objectively measure the analgesic effects of opioid medications.