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ORIGINAL ARTICLE

Evaluation of pupil diameter for pain assessment in interventional headache management

Girişimsel tedavi uygulanan baş ağrılarında pupil çapının değerlendirilmesi

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Summary

Objectives: Pain is a subjective experience. Besides, sensory, affective and behavioral responses, and autonomic response are part of pain response to noxious stimuli. Evaluation of pupil diameter by pupillometry has been used as an alternative method for pain assessment. In algologic procedures like interventional headache management have not been addressed in the literature. Herein, we investigated changes in pupil diameter during interventional headache management as an objective method for pain assessment.

Methods: Demographic data of the patients were collected before the bilateral major occipital nerve blockage (MONB) procedure. Numeric rating score (NRS) and pupil diameter measurements by pupillometer were recorded before MONB. Standard MONB procedure was applied to all patients. Pain assessment and pupillary diameter measurements were obtained after nerve blockage.

Results: Twenty-eight patients were included in this study. Mean age was 41.03±12.63 years. There is no difference between the hemodynamic parameters before and after the procedure. Post-procedure NRS and pupil diameter values were significantly lower than pre-procedure values. There was a positive correlation between changes in NRS scores and changes in the right and left pupil diameters.

Conclusion: There was a significant correlation between NRS score and pupil diameter in patients who underwent MONB. Monitoring of pupil diameter can be used for pain assessment during headache treatment. Evaluation of pupil diameter is a new approach in pain palliation. Future research is needed to study the effect of other parameters, that is, gender, age, origin of pain, acute, and chronic pain on pupil diameter and to evaluate its application in different algological procedures.

Keywords: Assessment of pain; major occipital nerve block; pain; pupil diameter; pupillometer.

Özet

Amaç: Ağrı, öznel bir deneyimdir. Duyusal, duygusal ve davranışsal tepkilerin yanı sıra otonomik tepki, ağrılı uyaranlara verilen tepkinin bir parçasıdır. Pupil çapının pupillometre ile değerlendirilmesi, ağrı değerlendirmesi için alternatif bir yöntem olarak kullanıldı. Bu çalışmada, girişimsel baş ağrısı yönetimi sırasında ağrı değerlendirmesi için pupil çapındaki değişiklikler araştırıldı.

Gereç ve Yöntem: Bilateral majör oksipital sinir blokajı (MONB) işlemi öncesi hastaların demografik verileri toplandı. Numerik derecelendirme puanı (NRS) ve pupillometre ile göz bebeği çapı ölçümleri, MONB'den önce kaydedildi. Tüm hastalara standart MONB prosedürü uygulandı. Sinir blokajı sonrası ağrı değerlendirmesi ve pupil çapı ölçümleri alındı.

Bulgular: Çalışmaya 28 hasta dahil edildi. Hastaların yaş ortalaması 41,03±12,63 yıl idi. İşlem öncesi ve sonrası hemodinamik parametreler arasında fark yoktu. İşlem sonrası NRS ve göz bebeği çapı değerleri işlem öncesi değerlerden önemli ölçüde düşüktü. NRS puanlarındaki değişiklikler ile sağ ve sol göz bebeği çaplarındaki değişiklikler arasında pozitif bir ilişki vardı.

Sonuç: MONB uygulanan hastalarda NRS skoru ile göz bebeği çapı arasında anlamlı bir ilişki vardı. Baş ağrısı tedavisi sırasında ağrı değerlendirmesi için göz bebeği çapının izlenmesi kullanılabilir. Pupil çapının değerlendirilmesi ağrı palyasyonunda yeni bir yaklaşımdır. Cinsiyet, yaş, ağrının kaynağı, akut ve kronik ağrı gibi diğer parametrelerin göz bebeği çapı üzerindeki etkisini incelemek ve farklı algolojik prosedürlerde uygulanmasını değerlendirmek için gelecekteki araştırmalara ihtiyaç vardır.

Anahtar sözcükler: Ağrı; ağrının değerlendirilmesi; pupil çapı; pupillometre; majör oksipital sinir bloku.

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Introduction

Pupillary diameter, iris size, is controlled by the activities of antagonistic muscles; sphincter pupillae and dilator pupillae. Sphincter pupillae, innervated by the cholinergic fibers of the parasympathetic system, leads to pupillary constriction. In contrast, dilator pupillae is innervated by the adrenergic fibers of the sympathetic system which leads to pupillary dilatation. As a result of the opposing activities and innervations of these muscles, pupil dilation is used as an index for sympathetic system activity. Pupillary dilation reflex (PDR) is a robust reflex that controls pupil diameter in response to light intensity. Auditory and painful stimuli mediate pupil dilatation in awake subjects by sympathetic activation of dilatator muscle.[1] Changes in pupillary diameter are clinically associated with pain and pupillometric measurements can be used to evaluate analgesics efficacy in in anesthesia practice.[2,3]

Pain is a subjective experience. Besides, sensory, affective and behavioral responses, and autonomic response are part of pain response to noxious stimuli.[4] Sympathetic system activation results in increased heart rate, tachypnea, and pupil dilatation as a response to noxious stimuli.[5] Recent advances in technological capabilities have enabled the measurement of pupil diameter and pain evaluation. Evaluation of pupil diameter by pupillometry have been used as an alternative method for pain assessment.[6–9] Measurement of pupil diameter in algologic procedures like interventional headache management have not been addressed in the literature. Herein, we investigated changes in pupil diameter during interventional headache management as an objective method for pain assessment.

Material and Methods

Setting and Participants

Ethical approval for this study was obtained from (the Local Ethics Committee, Türkiye) (Number: 2021/3388) according to the Declaration of Helsinki.

Thirty patients older than 18 years who underwent bilateral major occipital nerve blockage (MONB) for headache treatment were enrolled in this study. Headache disorders are classified and diagnosed according to International Headache Society 2018 guidelines[10] and patients who had primary headache included in the study. Patients younger than 18 years, abnormal pupil reading, or abnormal pupil reactivity according to neurological pupil index (NPI), patients who had a history of substance abuse and addiction, secondary headache, psychiatric disorders, intracranial pathologies, motor deficits, periorbital or facial edema, ocular disease, anticholinergic drug usage, deteriorating condition, high morbidities or orientation-coordination problems, and patients who underwent emergent procedures were excluded from this study.

Informed consent including detailed information about the procedure was obtained from each participant. Information concerning the trial was explained both orally and in a written form to all patients and a written consent form was signed by each patient. Demographic data of the patients were collected before the procedure. Numeric rating score (NRS) and pupil diameter measurements by pupillometer (Pupillometer NPi-200, NeurOptics, USA) were recorded before MONB. Standard MONB procedure was applied to all patients. Pain assessment and pupillary diameter measurements were obtained 5 min after nerve blockage.

MONB

MONB was performed in each patient by the same anesthesiologist using the same technique. Hemodynamic measurements (heart rate, blood pressure, and pulse oximetry) were recorded. Ultrasound-guided nerve block was applied in the sitting position after appropriate skin disinfection. Local anesthesia was applied using 25-gauge needle after locating the occipital artery and nerve. 7.5 mg (0,375%) bupivacaine, 10 mg (1%) prilocaine, and 2 mg dexamethasone were used for local anesthesia. Ultrasound was used for visualizing local anesthetic solution delivery to ensure proper distribution.

Evaluation of Pupil Diameter

During the measurements, portable infrared pupillometer device (Pupillometer NPi-200 ™, NeurOptics, USA) was used to assess pupil diameter. Pupil diameter and NPI values were measured automatically with the pupillometer. Since pupil diameter can vary depending on ambient illumination and the point at which the patient focuses his gaze, scotopic conditions were provided to optimize the measurements.

Table 1. Hemodynamic values of patients, before and after major occipital nerve block (n=28)

	Before MONB (mean±SD)	After MONB (mean±SD)	p
Heart rate (beat/min)	85.07±17.96	85.29±15.88	0.967
Peripheral oxygen saturation (%)	95.75±2.44	97.43±3.52	0.062
Systolic blood pressure (mmHg)	155.39±21.98	157.25±20.73	0.763
Diastolic blood pressure (mmHg)	91.14±11.09	91.54±10.08	0.904
Mean blood pressure (mmHg)	113.82±13.49	115.54±12.40	0.679

MONB: Major occipital nerve block; SD: Standard deviation; *: P<0.05 is statistically significant.

Table 2. Comparison of pupil diameter, NPI, and NRS

	NRS (Mean±SD)	Pupil diameter		NPI	
		Right (Mean±SD)	Left (Mean±SD)	Right (Mean±SD)	Left (Mean±SD)
Before MONB	3.82±2.63	4.76±1.08	4.64±1.08	4.04±0.46	4.06±0.46
After MONB	1.60±1.66	4.18±1.13	4.03±1.08	4.21±0.36	4.27±0.33
p-value	*<0.001	*0.006	*0.003	*0.008	*0.006

MONB: Major occipital nerve block; NPI: Neurological Pupil Index; NRS: Numeric Rating Scale; SD: Standard deviation; *: P<0.05 is statistically significant.

Table 3. Correlation analysis between numeric rating scale change and right and left pupil diameter changes

	1	2	3
1. NRS change			
r	1	0.464**	0.465*
p		**0.013****	**0.013****
2. Right pupil diameter changes			
r		1	0.837**
p			<**0.001****
3. Left pupil diameter changes			
r			1
p			

*: The correlation is significant at the 0.05; **: The correlation is significant at the 0.01; ***: P<0.05 is statistically significant.

The light-insulated silicone collar of the device isolated the measured eye from ambient light. The opposite side of the eye was closed with a thick cover and isolated. Besides, hemodynamic measurements, pre- and post-procedure measurements of NRS score, and left and right pupil diameter were recorded. The NPI measurement range is 3.0–4.9 and results out of this range are considered abnormal pupil reactivity. Furthermore, a difference in NPI between right and left pupils of ≥0.7 can also be considered an abnormal pupil reading.

Statistical analysis

Data were analyzed using SPSS 18.00 (the Statistical Package for the Social Sciences, Inc., Chicago, IL). Continuous variables were presented as mean±standard deviation and percentages (%). Categorical variables were presented as numbers and percentages. Kolmogorov–Smirnov test was used for testing normal distribution of the data. Mann–Whitney U-test was used for analyzing continuous variables. Dependent t-test was used for repeated measures. p-values <0.05 (p<0.05) were considered statistically significant.

Results

Thirty patients (between 18 and 76 years) were included in this study. Two patients were excluded since the difference between NPI measurements was higher than 0.7. Of these subjects, ten were male and 18 were female. Mean age was 41.03±12.63 years. Except of headache, 20 patients (71.4%) had no other underlying comorbidities. Hemodynamic parameters before and after the procedure are summarized in Table 1. Post-procedure NRS and pupil diameter values were significantly lower than pre-procedure values. Pupil diameter, NPI, and NRS scores are summarized in Table 2. There was a positive correlation between changes in NRS scores and changes in the right and left pupil diameters (Table 3).

Discussion

A decrease in pupil diameter was associated with pain palliation in patients who underwent MONB for headache treatment.

Headache is a very common condition among adults. Headache disorders are classified and diagnosed according to International Headache Society 2018 guidelines.[10] Headache disorders impose a noticeable burden including impaired quality of life, productivity impairment, and reduced daily-life activity.[11,12] Chronic headache was associated with impaired quality of life, reduced workplace productivity, and work absenteeism in the previous reports.[13–15] Lack of knowledge among health-care providers regarding effective treatment modalities and underestimation of pain by patients hinders proper management of headache. In addition to effective treatment options, objective methods for evaluating treatment effectiveness are required. In this study, the diagnosis and classification of headache was planned according to the International Headache Society Guidelines-2018. The primary headache patients were included in the study.

MONB is a procedure involving injecting local anesthetics to block the afferent signals from sensory regions innervated by major occipital nerve.[16] MONB is a widely used peripheral nerve block procedure for headache treatment.[17] Combination of bupivacaine or lidocaine and corticosteroids was associated with rapid-onset anesthesia and reduced pain intensity and duration.[18–22] Patients who underwent MONB in daily clinical practice were included in our study.

PDR is a sympathetic reflex that mediates pupillary dilatation in response to painful stimuli.[23] Measurement of pupil diameter was used for evaluating anesthetic agents during general anesthesia. Larson et al.[24] showed that alfentanil attenuates PDR in response to noxious stimuli. Negative correlation was detected between plasma alfentanil concentrations and pupillaray dilation degree.[24,25] Similarly, increased remifentanil concentrations were associated with decreased PDR in healthy subjects under propofol anesthesia. PDR changes were prominent than changes in hemodynamic parameters in children under sevofluran and 50% nitric oxide anesthesia.[2,26–28]

Pupillometric monitorization reduced intraoperative remifentanil and post-operative morphine consumption in a randomized controlled study.[29] Pupillometric monitorization can be used as a reliable method to evaluate post-operative analgesia and as an index for pain intensity.[6] Unlike previous studies, we included patients who applied with headache complaint to algology clinic in our study. We detected a decrease in NRS scores and pupil diameter in patients who underwent MONB for headache treatment. There was a positive correlation between changes in pupil diameter and NRS scores. These results are compatible with the previous reports on the relation between pain and pupil diameter in perioperative settings.

Analysis of pupillary functions with infrared pupillometry reduces observer bias, enables noninvasive evaluation of pupil dimensions and reactivity, and ensures reliable repeatability of measurements. NPI scores above 3 are considered normal. Scores below 3 indicates abnormal/sluggish pupillary reflex, while 0 score indicates non-reactive or atypical pupillary reflex. A difference in NPI of 0.7 or more between right and left pupil measurements reduces the reliability of measurements and decreases NPI values response to noxious stimuli.[8,30,31] Two patients were excluded from our study since NPI difference was >0.7 in consecutive measurements. We also noticed a decrease in NRS scores and an increase in NPI scores after nerve block.

Appropriate diagnosis and management of pain begins with proper evaluation of patient's pain. Regular monitoring is essential for the evaluation of pain intensity and treatment response. Patient's report of pain and hemodynamic parameters, that is, heart rate and blood pressure are used while monitoring pain.[32] There was no significant change in hemodynamic parameters before and after nerve block, while there was a significant decrease in NRS scores and pupil diameter in our patients. Other parameters may be inadequate and measurement of pupil diameter can be used as an alternative method for pain assessment. Our findings suggest that pupillometry use in pain management protocols may facilitate objective measurement of pupil diameter and can be used in clinical practice.

Baseline pupil diameter can be affected by the interaction between the sympathetic and parasympathetic nervous systems and several factors such as ambient light, visual compliance, and drug interactions. Although there was no relationship between baseline pupil size and first NRS score, a significant correlation between analgesia and changes in pupil diameter was previously reported.[6,33] We avoided using antiemetics such as dopaminergic receptor antagonists and anticholinergic drugs in our patients due to their effects on pupil diameter. To minimize measurement errors, pre-procedure and post-procedure measurements were taken in the same environment and completed by the same anesthesiologist.

There is no evidence of the effect of local anesthetics on pupil diameter. Pupil diameter was not affected in patients who received regional anesthesia-analgesia and was suggested as a reliable method for pain assessment.[34]

There were many limitations in this study. Although it is easy to measure pupil diameter with pupillometry, it is prone to practitioner errors. Simultaneous measurement of NPI scores obtained during pupil diameter measurement can be used to evaluate the reliability of the measurements. Data of two patients were outside predetermined reference values and were excluded from analysis. The aim of this study was to evaluate outpatients; thus, it was difficult to standardize study group. Patients with acute and chronic headache were enrolled in this study, so we were unable to evaluate the difference between these groups. Finally, Although the effect of anxiety on pain perception is widely discussed, there is no consensus in the literature.[35–39] However, individuals with moderate-to-severe anxiety have been reported to have larger pupil diameters than those with or without mild anxiety.[40] However, in this study, the anxiety level of the patients was not evaluated during pupil measurements.

Conclusions

There was a significant correlation between NRS score and pupil diameter in patients who underwent MONB. Monitoring of pupil diameter can be used for pain assessment during headache treatment. Evaluation of pupil diameter is a new approach in pain palliation. Future research is needed to study the effect of other parameters, that is, gender, age, origin of pain, acute, and chronic pain on pupil diameter and to evaluate its application in different algological procedures.

Ethics Committee Approval: The Necmettin Erbakan University Clinical Research Ethics Committee granted approval for this study (date: 03.09.2021, number: 2021/3388)

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