SCIENTIFIC REPORT

The sensitivity and specificity of 0.5% apraclonidine in the diagnosis of oculosympathetic paresis

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Aims: To evaluate the sensitivity and specificity of 0.5% apraclonidine test in the diagnosis of oculosympathetic paresis (OSP).

Method: Apraclonidine (0.5%) was administered to 31 eyes, nine with a diagnosis of Horner syndrome (HS), 22 with bilateral OSP caused by diabetes, and to 54 control eyes. All were confirmed with the cocaine test. The effects on pupil diameter and upper eyelid level were observed 1 hour later.

Results: Apraclonidine caused a mean dilation of 2.04 mm (range 1–4.5) ($p<0.001$) in the pupils with OSP and it caused pupillary constriction in the control eyes with a mean change of −0.14 mm (range 0.5 to −1) ($p<0.05$). It caused reversal of anisocoria in all HS cases. Its effects on both pupil diameters and upper lid levels differed significantly between the groups ($p<0.001$). The mean elevation in the upper lid was 1.75 mm (range 1–4) in the OSP group ($p<0.001$) and 0.61 mm (range 0–3) in the control group ($p<0.001$).

Conclusion: The effect of the apraclonidine (0.5%) test on the pupil diameter was diagnostic for OSP and had at least the same sensitivity and specificity as the cocaine test for the diagnosis of OSP.

Lesions along the sympathetic pathway to the eye produce oculosympathetic paresis (OSP). Unilateral OSP have been classically named Horner syndrome (HS). Bilateral OSP is rare, reported in cervical spinal cord injuries and in diabetic patients as a part of systemic autonomic diabetic neuropathy.[1–3] Clinical findings in both HS and bilateral OSP can be very subtle. Pharmacological diagnosis with the use of topical cocaine and hydroxyamphetamine has been a standard approach for years. However, cocaine is a controlled substance which is difficult to obtain and hydroxyamphetamine is not easily available in most countries. Recently, apraclonidine, an α_2 agonist, has been found to dilate pupils in HS, in spite of the fact that it has minimal effect on pupils in normal eyes.[4] It was studied in a limited number of patients and found useful for the diagnosis of HS.[4–6] Apraclonidine is commercially available for glaucoma treatment and it will be very helpful if it can be used in the diagnosis of OSP. In this study we tried to assess the sensitivity and specificity of the apraclonidine test in the diagnosis of HS and bilateral OSP by comparing its effects on pupil diameter and upper lid level, in eyes with cocaine confirmed OSP and normal eyes.

MATERIALS AND METHODS

This study was done under the approval of our institutional ethics committee and consent was taken from each patient before the test administration.

Twenty patients (31 eyes; nine unilateral and 11 bilateral), who had cocaine confirmed diagnosis of OSP and agreed to participate in the study, were scheduled to have a 0.5% apraclonidine test. No other aetiology could be found in 12 patients except diabetes mellitus. The onset of OSP was not certain in most of the cases, but all had a long duration of the disease (>3 months). Twenty three normal volunteers (46 eyes) were also recruited to the study. Subjects were excluded from the control group if they had an active ocular infection, past or present ocular pathological condition, unstable cardiovascular disease, diabetes mellitus, previous intraocular surgery, had worn contact lenses within 3 days before starting the study, and taken any systemic adrenergic medication within 15 days of the test administration. Four of the control subjects had physiological anisocoria; two of them were tested with cocaine and had equal dilation in both eyes. Eight unaffected eyes of nine cases with HS were also included into the control group.

Baseline pupil diameters were determined to the nearest 0.5 mm using the pupil gauge on the Rosenbaum pocket vision screener, in normal room lighting and with the room lights off. The amount of ptosis was determined by measuring the vertical fissures on both sides and taking the difference in unilateral cases. In bilateral cases, it was determined by measuring the amount of cornea covered by the upper lid and then subtracting 2 mm. Pictures were taken with a digital camera in the same position and lighting condition before and 1 hour after one drop of 0.5% apraclonidine instillation into each eye. The same pupil and lid measurements were also taken 60 minutes after apraclonidine instillation. Pupillary diameter and upper lid level changes caused by apraclonidine were compared within the groups and between the groups.

For statistical analysis; χ^2, two independent samples T and paired samples T tests were used.

RESULTS

Groups were not different with respect to age and sex distribution. The mean ages were 52 (SD 11) years in the OSP group and 48 (SD 11) years in the control group ($p>0.05$, independent sample *t* test). Female/male ratio was 12/19 for the OSP group and 22/32 for the control group ($p>0.05$, χ^2 test). All patients with bilateral OSP had at least 1 mm pupillary dilation and all unilateral cases had reversal of anisocoria following apraclonidine instillation. Changes caused by apraclonidine was found to be significant for both pupil diameter and lid level ($p<0.001$) (table 1). The effect of apraclonidine on the pupils of control eyes was minimal, symmetrical, and in the constriction direction in most of the eyes, if any change was observed when compared with its effect on the eyes with OSP ($p<0.001$) Minimal (0.5 mm) asymmetric response occurred in only one case in the control group. The mean change in control pupils caused by apraclonidine was found to be −0.14 mm (range 0.5 to −1) but this change was still significant ($p<0.05$). Apraclonidine

Abbreviations: HS, Horner syndrome; OSP, oculosympathetic paresis

Table 1 Pupil size and upper lid level changes (SD) (mm) of the groups

	OSP group (n = 31)			Control group (n = 54)		
Variable (mm)	Baseline (range)	Apraclonidine (range)	p Value	Baseline (range)	Apraclonidine (range)	p Value
PS	2.33 (0.47) (2–4)	4.38 (1.06) (3–8)	<0.001	3.09 (0.70) (2–4.5)	2.94 (0.54) (2–4.5)	<0.05
PD	2.04 (0.83) (1–4.5)			−0.14 (0.45) (−1–0.5)		<0.001
Ptosis	1.35 (0.75) (0–3)	−0.40 (0.89)* (0– (−3))	<0.001	0.19 (0.51) (0–2)	−0.41 (0.79)* (0–(−3))	<0.001
LR	1.75 (1.00) (0–4)			0.61 (0.82) (1–3)		<0.001

PS, pupil size; PD, pupil difference; LR, lid retraction.
*Retraction with respect to the presumed normal upper lid level.

caused significant lid elevation in both the OSP and control groups ($p<0.001$). The patients displayed no adverse effects after the apraclonidine test.

Representative patients with unilateral OSP (HS), bilateral OSP, and pseudo-HS are shown in figures 1, 2, and 3, respectively.

DISCUSSION

Apraclonidine, an α_2 agonist, has been approved for use in reducing the intraocular pressure rise that may occur after anterior segment laser procedures.[7–9] α_2 Receptors were found both prejunctionally and postjunctionally in the nerve terminals; stimulation of prejunctional receptors inhibits the release of neurotransmitters and stimulation of postjunctional receptors inhibits the cellular responses to endogenous neurotransmitters and hormones.[10 11] Apraclonidine is normally expected to cause pupillary miosis in normal human subjects, but it also has the ability to stimulate α_1 adrenergic receptors, as is evidenced by conjunctival vasoconstriction, with a lower efficacy than noradrenaline.[4]

During a study for the location of its action for lowering the IOP, 1% apraclonidine was found to cause mydriasis in six eyes with HS.[4] The mydriatic effect, observed in eyes with HS, was explained by denervation hypersensitivity of α_1 receptors on the iris dilator muscles to apraclonidine in the absence of normal sympathethic tone.[4 12 13] In control eyes, mydriasis of 0.5 mm was noted in only one patient. Later, Bacal and Levy reported the utility of 1% apraclonidine without any adverse effects in the diagnosis of four paediatric patients with HS.[5] Brown *et al* tested 0.5% apraclonidine in eight patients with pharmacologically confirmed HS diagnosis.[6] They observed a reversal of anisocoria of at least 0.5 mm in both dark and light conditions in seven of the eight patients. They found the test 88% sensitive. The patient who could not show the reversal was not tested with cocaine but with hydroxyamphetamine.

There are studies on apraclonidine, mainly focused on its effect on the intraocular pressure, but also commenting about the effects on pupil diameter and upper lid level. Robin has studied 1% apraclonidine on normal volunteers.[14] Following the instillation of the drug, eyes treated with apraclonidine had progressively larger mean pupillary diameters than the contralateral, placebo treated eyes ($p<0.05$ at 1 hour, $p<0.01$ at 3 and 5 hours, and $p<0.005$ at 7 hours). Our patients were not observed for more than 1 hour and we specifically focused on the apraclonidine effect on pupil size and took photographs of any change. In our group 44% of the control eyes did not display any changes in pupillary size, 37% displayed miosis (0.5–1 mm), and 19% displayed mydriasis (0.5 mm). The overall change was 0.14 mm in the miosis direction. The difference in the findings could be explained by the utilisation of different concentration in our study. However, in the previous two studies on the utility of apraclonidine for the diagnosis of HS, 1% concentration had been used and a total of 14 normal eyes had the apraclonidine test; miosis (0.5–2 mm) had been observed in four eyes and no change had occurred in the rest.[4 5] Abrams *et*

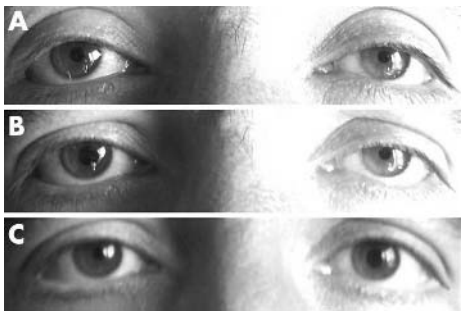

Figure 1 Horner syndrome in left eye. (A) Baseline condition, miosis and ptosis in left eye. (B) No change in the left eye 1 hour following 10% cocaine instillation. (C) Anisocoria reversal and lid elevation in the left eye 1 hour after instillation of 0.5% apraclonidine.

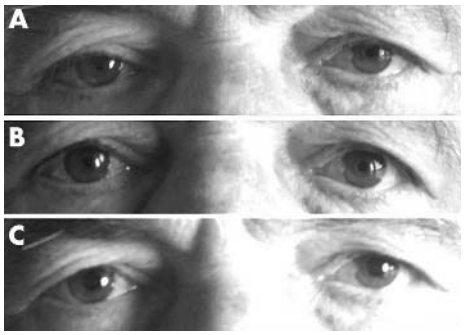

Figure 2 Bilateral OSP caused by diabetes mellitus. (A) Baseline condition, bilateral miosis and ptosis. (B) No change 1 hour later 10% cocaine instillation. (C) Bilateral dilation and lid elevation 1 hour after instillation of 0.5% apraclonidine.

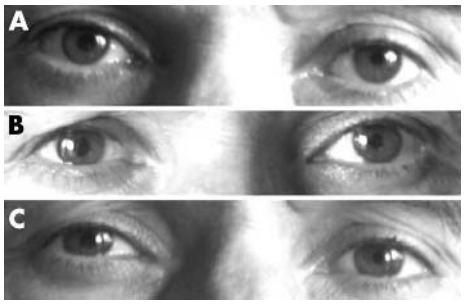

Figure 3 Pseudo-Horner syndrome. (A) Baseline anisocoria. (B) Symmetrical dilation of both pupils 1 hour after 10% cocaine instillation. (C) Symmetrical bilateral miosis 1 hour after instillation of 0.5% apraclonidine.

al used 1% apraclonidine on normal volunteers and did not report any significant changes in the pupil diameters.[15] Jampel and Stewart used 0.5% and 0.25% concentrations of apraclonidine on glaucoma patients.[16 17] They found a dose dependent increase in the lid retraction but did not observe any significant pupillary effect.

Apraclonidine caused significant lid elevation in most of the patients with OSP (87%); however, this effect was not specific to the OSP, because it also had the same effect in 45% of normal control eyes. The lid elevation effect could not be used as a diagnostic indication for OSP or HS; however, it can be useful in long term symptomatic relief of patients with HS affected by their ptosis.

Apraclonidine (0.5%) caused a mean 2.04 mm (1–4.5) dilation 1 hour after the instillation, in eyes with OSP. It did not cause more than 0.5 mm dilation in any of the control eyes. We conclude that the 0.5% apraclonidine test has at least the same sensitivity and specificity as the cocaine test for the diagnosis of OSP.

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This study was conducted in Hacettepe University Hospitals and SB Ulucanlar Eye Hospital, under the approval of our institutional ethic committee.

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