CLINICAL STUDY

The acute effect of pilocarpine on pulsatile ocular blood flow in ocular hypertension

M.H. SHAIKH, J.S. MARS

Abstract

Purpose **To determine the acute effects of application of 2% pilocarpine on pulsatile ocular blood flow.**

Methods **In a randomised prospective controlled study of an exploratory nature, 18 subjects with ocular hypertension had pilocarpine 2% eye drops instilled into a randomly chosen eye three times at 10 min intervals. Physiological saline was instilled into the contralateral control eye. Intraocular pressure (IOP) and pulsatile ocular blood flow (POBF) measurements were taken before the first application and 90 min after the last application using the OBF tonometer (OBF Laboratory, Wilts, UK). Statistical analysis was performed using the Wilcoxon signed rank test.**

Results **Of the 18 patients who entered the trial, 2 were suggested by the OBF system software as having 'poorly reliable' data. The analysis was made on the remaining 16. There was a significant reduction in IOP at 90 min for the treated eye in comparison with the contralateral control eye ($p = 0.001$; median difference −4.25 mmHg; 95% confidence interval, −5.85 to −2.40). There was a significant increase in POBF at 90 min in the treated eye in comparison with the contralateral control eye ($p < 0.001$; median difference 4.60 μl/s; 95% confidence interval, 2.35 to 6.75).**

Conclusion **Acute application of pilocarpine 2% drops increased POBF to a significant extent in untreated ocular hypertension.**

Key words Intraocular pressure (IOP), Ocular hypertension (OHT), Pilocarpine, Primary open angle glaucoma (POAG), Pulsatile ocular blood flow (POBF)

While reduction in the intraocular pressure (IOP) remains the *sine qua non* of medical therapy for glaucoma, the aetiology of glaucoma is increasingly recognised as multifactorial. Reduced optic nerve perfusion is suggested as a pathogenetic mechanism in both normotensive and primary open angle glaucoma.[1] For this reason it is essential to know the ocular haemodynamic as well as hypotensive effects of glaucoma medications.

The ocular blood flow (OBF) system (OBF Laboratory, Wilts, UK) is a highly sensitive pneumotonometer linked to a data acquisition unit, which measures IOP change non-invasively with a collection rate of 200 Hz, allowing quick and reproducible measurement of the ocular pulse amplitude and pulsatile ocular blood flow (POBF).[2]

Although currently superseded by the newer agents in many units, pilocarpine remains a useful drug in the management of open angle glaucoma. Compared with other hypotensive agents, pilocarpine significantly reduces IOP in most patients, causing relatively few adverse effects. Whereas newer antiglaucoma drugs are extensively studied with regard to their effect on blood flow in the eye, time-honoured pilocarpine has not received its due attention. Reports in the literature about the effects of pilocarpine on POBF dynamics draw diverging conclusions. Carenini *et al.*[3] had shown an increase in pulsatile ocular blood flow with pilocarpine 2% and 4% in patients with open angle glaucoma. However, Schmidt *et al.*[4] studying the effect of various antiglaucoma drugs on ocular pulse amplitude in a small series of 6 ocular hypertensives, noticed a significant reduction following a single dose application of 4% pilocarpine. In view of the apparently conflicting nature of the evidence, we designed a randomised-controlled study of an exploratory nature to assess the acute haemodynamic effects of pilocarpine in untreated ocular hypertensives.

Materials and methods

Consecutive patients with ocular hypertension attending the glaucoma clinic between February 1999 and May 1999 were enrolled in the study. The subjects were on no antiglaucoma medication and had open angles on gonioscopy. Those with concomitant eye disease, previous eye surgery or refractive error of more than 3 dioptres were excluded from the study. Patients with systemic vascular diseases (such as

M.H. Shaikh
J.S. Mars
Department of Ophthalmology
Royal Albert Edward Infirmary
Wigan
UK

J.S. Mars ✉
Department of Ophthalmology
Royal Albert Edward Infirmary
Wigan Lane
Wigan WN1 2NN, UK
Tel: +44 (0)1942 822468
Fax: +44 (0)1942 822587
e-mail: simonmars@compuserve.com

Commercial or proprietary interests: None

Received: 22 February 2000
Accepted in revised form: 15 August 2000

Table 1. *Descriptive statistics of intraocular pressure in treated and control eyes*

	Intraocular pressure (mmHg)					
	Treated eyes			Control eyes		
	Baseline	90 min	Change	Baseline	90 min	Change
Number	16	16	16	16	16	16
Mean ± SD	26.1 ± 3.6	22.9 ± 3.8	−3.2 ± 4.8	24.9 ± 3.9	25.8 ± 3.1	0.9 ± 3.6
Median	24.9	23.25	−3.35[a]	23.45	25.6	1.35[b]
Percentile (25, 75)	23.6, 29.95	20.1, 25.9	−0.55, −5.1	22.4, 28.0	24.8, 28.3	−0.9, 3.4

[a] $p = 0.02$ (Wilcoxon signed rank test); [b] $p = 0.30$ (Wilcoxon signed rank test).

diabetes, hypertension) and those on cardiovascular medications (beta-blockers, vasodilators) were also excluded.

The OBF tonometer system (OBF Laboratory, Wilts, UK) was utilised for the purpose of obtaining IOP and POBF measurements. The baseline IOP and POBF were determined in the sitting position using the OBF tonometer. Using the randomised permuted block method, each patient's randomly chosen eye was assigned to receive pilocarpine 2% drops three times at 10 min intervals. The contralateral control eye correspondingly received physiological saline drops. Ninety minutes after the last application, the measurements were repeated. The same examiner took all measurements. Both eyes of each subject were tested, the right eye first. Due to obvious difficulties in masking the miotic effect of pilocarpine, the study design was not masked.

The study protocol was accepted by the Wigan and Leigh NHS Trust ethics committee. Informed consent was obtained for each patient following complete explanation of the procedure.

Since there was some evidence of skewness of the data, a non-parametric statistical method in the form of the Wilcoxon signed rank test was employed. Five per cent was considered as the level of significance.

Results

Of 18 patients who entered the trial, 2 had 'poorly reliable data' as suggested by the OBF system computer software. The final analysis was done on 16 patients. Their mean age was 67 years (range 58–79 years). Nine of 16 (58%) were women.

IOP decreased significantly in the pilocarpine-treated eyes at 90 min ($p = 0.02$; Table 1). The change in the contralateral control eyes was statistically not significant. POBF increased significantly in pilocarpine-treated eyes at 90 min ($p = 0.01$; Table 2). The change in the contralateral control eyes was statistically not significant.

The difference in the change in IOP (comparison between the treated and control eyes) was significant ($p = 0.001$; Table 3). The difference in the change in POBF (comparison between the treated and control eyes) was also significant ($p < 0.001$; Table 3). This suggests that pilocarpine increased POBF significantly.

Discussion

The idea that IOP alone does not account for the development of all glaucomatous optic neuropathy is now commonly accepted. Vascular factors including altered ocular blood flow and optic nerve perfusion appear to be important. It is therefore imperative that antiglaucoma agents are evaluated for their haemodynamic as well as their hypotensive effect.

In our study, the acute application of pilocarpine 2% drops decreased IOP significantly at 90 min. It also produced a significant increase in POBF. As we used the patient's contralateral eye as a control, systemic variables such as heart rate and systemic pressure are not relevant to the conclusion. The increase in POBF observed in our study may be the indirect result of a decrease in IOP, which in turn could lead to an increase in perfusion pressure. However, the current antiglaucoma drugs that reduce IOP do not necessarily increase ocular blood flow.[5] This is possibly due to reactive vasoconstriction secondary to the fall in IOP, tending to produce the effect in the opposite direction.[6]

The muscarinic parasympathetic fibres, which are known to be vasodilatory in function, richly supply both the choroidal circulation and ciliary arteries.[7] In rabbits and cats, intra-arterial injection of acetylcholine causes an increase in choroidal blood flow.[8] In monkeys, atropine abolishes pilocarpine-induced uveal vasodilatation, suggesting the effect is mediated through vascular muscarinic receptors.[9] In this context it is interesting to note that in human volunteers a significant reduction in POBF that is independent of pupillary changes is

Table 2. *Descriptive statistics of pulsatile ocular blood flow in treated and control eyes*

	Pulsatile ocular blood flow (μl/s)					
	Treated eyes			Control eyes		
	Baseline	90 min	Change	Baseline	90 min	Change
Number	16	16	16	16	16	16
Mean ± SD	16.9 ± 8.4	19.5 ± 8.6	2.6 ± 3.6	17.8 ± 8.0	15.7 ± 5.6	−2.2 ± 4.9
Median	13.7	20.15	2.05[a]	14.1	2.05	−1.15[b]
Percentile (25, 75)	10.9, 20.5	12.8, 22.1	0.9, 4.8	12.4, 23.7	11.3, 17.9	−1.85, 1.3

[a] $p = 0.01$ (Wilcoxon signed rank test); [b] $p = 0.10$ (Wilcoxon signed rank test).

Table 3. *Difference in the change between the treated and control eyes*

Parameter	Median of the difference in the change	95% confidence interval	*p* value (Wilcoxon signed rank test)
Intraocular pressure (mmHg)	−4.25	−5.85 to −2.40	0.001
Pulsatile ocular blood flow (μl/s)	4.6	2.35 to 6.75	< 0.001

reported to occur following the application of antimuscarinic agents such as tropicamide and cyclopentolate.[10]

In light of the above considerations and assuming that the topical pilocarpine does not have significant effects on systemic vascular haemodynamics, it is possible that the beneficial effect of pilocarpine on the ocular blood flow may be a direct choroidal vascular action. The extent to which choroidal diffusion of the drug takes place in humans is unknown. In rabbits, penetration into the posterior segment is indicated by the observation of rising levels of pilocarpine in the vitreous within the first hour of its topical application.[11]

The results of our study are paralleled in the ocular hypertensive rabbits by the significant increase in ocular blood flow (as measured by the microsphere technique) observed at 60 min after the acute application of 1% pilocarpine.[12] In a small group of 6 ocular hypertensive human subjects, Schmidt *et al.*,[4] however, noticed a reduction in the ocular pulse amplitude following a single application of a drop of 4% pilocarpine. The fact that we employed more intensive acute application, instilling the drops three times at 10 min intervals, could have affected the ocular pharmacokinetics more favourably. Our randomised-controlled study provides the first evidence of the beneficial effects of the acute application of pilocarpine on POBF in untreated ocular hypertensives.

An acute effect as shown in this study may not necessarily be a predictor of the long-term effect. With continued treatment, pilocarpine is known to accumulate in the cornea, which in turn acts as a reservoir for the drug.[13] The IOP lowering effect of pilocarpine is therefore greater on chronic administration than on acute application.[14] A similar phenomenon with regard to its POBF improving property remains to be documented.

Further, the beneficial effect of pilocarpine on POBF in ocular hypertensives as observed in our study cannot necessarily be extrapolated to primary open angle glaucoma (POAG) patients, who are known to have different ocular haemodynamics.[15] Moreover, POBF response to the treatment is known to vary between individual patients.[16] Whereas this might be the fault of the technique, POAG may be a heterogeneous entity,[17] with different patients showing different vascular response to the disease and its treatment.

In agreement with our study, Carenini *et al.*[3] did find an increase in POBF with pilocarpine 2% and 4% in individuals with chronic open angle glaucoma; with the 4% gel producing a greater effect than the 2% aqueous preparation. The evidence exists that timolol, a commonly used first-line drug in the treatment of POAG, reduces POBF,[18] possibly due to its vasoconstrictive property.[19] The beneficial haemodynamic effect of adjuvant therapy with a parasympathetic vasodilator such as pilocarpine is therefore theoretically conceivable in patients receiving timolol. Claridge,[16] however, did not notice any such effect on POBF from the treatment with 2% pilocarpine drops. Larger prospective trials are required to reveal the net haemodynamic effects of pilocarpine used in conjunction with various antiglaucoma agents.

The conclusion of our study is not complete without consideration of the limitations of the techniques used. The OBF system measures the pulsatile component of the total ocular blood flow. It fails to take into account the changes occurring in non-pulsatile ocular blood flow. The calculation of POBF from a pressure/volume relation is based on number of assumptions.[20] Moreover, POBF is largely determined by the changes in the choroidal blood flow, of which optic nerve circulation constitutes only a small part. Furthermore, there is evidence that this critical region is subjected to its own autoregulation.[21] Presently there is no single method for assessment of all the crucial aspects of the circulatory status of the human optic nerve. The collective use of various techniques of blood flow measurements, albeit with their own limitations, could give a more representative picture of the true haemodynamic changes at the optic nerve level.[6,11] Further studies on larger groups of glaucoma patients and utilising different techniques of ocular blood flow assessment could be helpful in arriving at a comprehensive conclusion about the true ocular haemodynamic effects of pilocarpine.

The use of pilocarpine in the management of pre-presbyopic patients is limited because of its intolerable side-effects, namely miosis and spasm of accommodation. However, in the treatment of glaucoma in elderly patients, pilocarpine has a special place due to it relative freedom from serious systemic side-effects. Pilocarpine-induced myopia often provides a welcome 'second sight' in these people. The incidence of normotensive glaucoma and systemic vascular risk factors including vasospasm is also more common in this age group. The ocular haemodynamics are a real concern in the management of such patients. Although currently available newer antiglaucoma agents offer a choice in many units, inexpensive pilocarpine could be the only option in the more limited therapeutic armamentarium of the developing countries. Our study serves to focus on the need for thorough evaluation and exploitation of the ocular haemodynamic effects of this longest-known antiglaucoma agent.

We gratefully acknowledge Dr Chris Robert, senior lecturer in medical statistics, Manchester University, for his expert advice on statistical matters.

References

1. Tielsch JM, Katz J, Sommer A, Quigley HA, Javitt JC. Hypertension, perfusion pressure and primary open glaucoma: a population based assessment. Arch Ophthalmol 1995;113:216–21.
2. Butt Z, O'Briens C. Reproducibility of pulsatile ocular blood flow measurement. J Glaucoma 1995;4:214–8.
3. Carenini AB, Brogliatti B, Gugliermina P, Rolle T. Flusso ematico oculare. Boll Ocul 1992;71(Suppl 4):3–63.
4. Schmidt KG, Stegman DY, Serle JB, *et al.* Ocular pulse amplitude in primary open angle glaucoma, low tension glaucoma, and in ocular hypertension patients before and after topical drug treatment. Invest Ophthalmol Vis Sci 1991;32(Suppl):943.
5. Schmidt KG, Ruckmann A, Pillunat LE. Topical carbonic anhydrase inhibitor increases ocular pulse amplitude in high tension primary open angle glaucoma. Br J Ophthalmol 1998;82:758–62.
6. Williamson TH, Harris A. Ocular blood flow measurement. Br J Ophthalmol 1994;78:939–45.
7. Bron AJ, Tripathi RC, Tripathi BJ. Wolff's anatomy of the eye and orbit, 8th ed. London: Chapman and Hall Medical, 1998.
8. Bill A. Autonomic nervous control of uveal blood flow. Acta Physiol Scand 1962;56:70–81.
9. Alm A, Bill A, Young FA. The effects of pilocarpine and neostigmine on blood flow through anterior uvea in monkeys: a study with radioactively labelled microspheres. Exp Eye Res 1973;15:31–6.
10. German EJ, Hurst MA, Wood D. Ocular blood flow variations with use of clinical ocular antimuscarinic agents. The second international symposium on experimental and clinical ocular pharmacology and pharmaceutics, Munich, 1997.
11. Sendelbeck L, Moore D, Urquhart J. Comparative distribution of pilocarpine in ocular tissues of the rabbit during administration by eye drop or by membrane-controlled delivery systems. Am J Ophthalmol 1975;80:274–83.
12. Chiou G, Chen YJ. Effects of antiglaucoma drugs on ocular blood flow inocular hypertensive rabbits. J Ocul Pharmacol 1993;9:13–24.
13. Van Hoose MC, Leaders FE. The role of cornea in the biologic response to pilocarpine. Invest Ophthalmol 1974;3:377.
14. Harris LS, Galin MA. Dose-response analysis of pilocarpine induced ocular hypotension. Am J Ophthalmol 1970;84:605.
15. Trew DR, Smith SE. Postural studies in pulsatile ocular blood flow. II. Chronic open angle glaucoma. Br J Ophthalmol 1991;75:71–5.
16. Claridge KG. The effect of topical pilocarpine on ocular blood flow. Eye 1993;7:507–10.
17. Brodway DC, Drance SM. Glaucoma and vasospasm. Br J Ophthalmol 1998;82:862–70.
18. Langham ME, Romeiko WJ. The unfavourable action of timolol on ocular blood flow and vision in glaucomatous eyes [abstract]. Invest Ophthalmol Vis Sci 1992;32(Suppl):1046.
19. Martin XD, Rabineau PA. Vasoconstrictive effect of topical timolol on human retinal arteries [see comments]. Graefes Arch Clin Exp Ophthalmol 1989;227:526–30.
20. James CB. Pulsatile ocular blood flow [editorial]. Br J Ophthalmol 1998;82:720–1.
21. Sossi N, Anderson DR. Effect of elevated intraocular pressure on blood flow. Arch Ophthalmol 1983;101:98–101.