

Dopamine and Intraocular Pressure in Critically Ill Patients

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Background: **A recently released dopamine-1 receptor agonist, fenoldopam, increases intraocular pressure (IOP) in both healthy volunteers and patients with chronic ocular hypertension. Dopamine, a potent agonist at both dopamine-1 and -2 receptors, is frequently infused in critically ill patients for its inotropic, renal vasodilatory, and natriuretic effects. The authors hypothesized that low doses of dopamine would significantly increase IOP.**

Methods: **Patients in the intensive care unit who were currently receiving dopamine infusions of less than 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ were studied. After local ocular anesthesia was obtained, baseline IOP was measured in each eye with a hand-held tonometer. IOP was then determined after dopamine was discontinued.**

Results: **Twenty-three patients received a mean dopamine infusion of 2.6 ± 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Twelve of the 23 patients were receiving mechanical ventilation during the study. Mean IOPs in nonventilated patients (n = 11) off dopamine were 13.1 ± 0.9 mmHg (left eye) and 12.6 ± 0.9 mmHg (right eye). Mean IOPs for the same patients receiving dopamine were significantly higher at 16.1 ± 0.9 mmHg (left eye) and 15.9 ± 1.1 mmHg (right eye). Mean IOPs in intubated patients (n = 12) off dopamine were 12.3 ± 0.7 mmHg (left eye) and 12.5 ± 1.2 mmHg (right eye). Mean IOPs for the same patients while receiving dopamine were significantly higher in intubated patients at 17.8 ± 1.3 mmHg (left eye) and 17.3 ± 1.3 mmHg (right eye). The average mean elevation in IOP in patients while receiving dopamine was significantly higher in intubated patients as compared with nonintubated patients (5.2 ± 0.9 mmHg *vs.* 3.1 ± 0.6 mmHg).**

Conclusions: **Commonly used doses of dopamine are associated with increased IOP in critically ill patients. Although normal patients should be able to tolerate this elevation safely for several weeks, there may be a potential risk in patients with preexisting glaucomatous nerve damage or ocular hypertension, especially if they are sedated and mechanically ventilated. (Key words: Catecholamine; complication; glaucoma; intensive care.)**

DOPAMINE is commonly used in critically ill patients for its vasopressive, inotropic, renal vasodilatory, and natriuretic effects. Dopamine is unique because of its dose-dependent stimulation of multiple receptors, including dopamine-1, dopamine-2, α-adrenergic, and β-adrenergic receptors. A recently released dopamine-1 agonist, fenoldopam, was noted to increase intraocular pressure (IOP) during clinical trials.[1,2] We hypothesized that dopamine would have a similar effect on IOP when used in critically ill patients.

Methods

After obtaining approval from the local institutional review board (Wake Forest University School of Medicine, Winston-Salem, NC), patients in the intensive care unit who were currently receiving dopamine infusions were recruited. A total of 40 patients were evaluated after obtaining written informed consent. Inclusion criteria were age between 18 and 65 yr and dopamine infusion less than 5 $mg \cdot kg^{-1} \cdot min^{-1}$ that was not being titrated to any hemodynamic end point. Exclusion criteria included a history of glaucoma, traumatic injury to the eye or significant corneal disease, any medications directed at the treatment of ocular hypertension, or a history of allergy to topical anesthetics. Patients were also excluded from further analysis if they were still receiving dopamine infusions after 4 days of observation (an arbitrary cutoff point) or if their ventilatory status (*i.e.*, extubated *vs.* intubated) changed during the observation period.

Local ocular anesthesia was obtained using one drop of proparacaine hydrochloride 0.5% in each eye. IOP was measured in each eye in duplicate using a Tono-PenXL (Bio-Rad, Glendale, CA). IOP was measured daily for up to 4 days by the same observer at the same time each day. Baseline IOP was determined after each patient had been off dopamine for at least 1 h, again at the same time of day as previous measurements.

Statistical Methods

Data were analyzed using a mixed-effects repeated measures analysis. Analysis was performed using SAS Proc Mixed software (SAS Institute, Inc., Cary, NC). A P value less than 0.05 was considered significant. Data are mean ± SEM.

Results

A total of 40 patients were studied. The data from 23 patients were used for statistical analysis. Seventeen patients were withdrawn from further evaluation either because they remained on a dopamine infusion beyond the 4-day observation period (n = 13) or because their

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Table 1. Mean Intraocular Pressure (mmHg ± SEM)

	Extubated (n = 11)		Intubated (n = 12)	
	Left Eye	Right Eye	Left Eye	Right Eye
Not administered dopamine	13.1 ± 0.9	12.6 ± 0.9	12.3 ± 0.7	12.5 ± 1.2
Administered dopamine	16.1 ± 0.9*	15.9 ± 1.1*	17.8 ± 1.3*	17.3 ± 1.3*
Increase	3.1 ± 0.7	3.3 ± 0.7	5.6 ± 1.4	4.8 ± 1.3

There were no significant differences between left and right eyes.

* $P < 0.05$ compared with patients not administered dopamine.

ventilatory status changed (n = 4) during the observation period (*e.g.*, from intubated to extubated). The average dose of the dopamine infusion was 2.6 ± 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (range, 1–3.75 $\mu g \cdot kg^{-1} \cdot min^{-1}$). The average age of the patients was 64.5 ± 6.3 yr. Approximately half of the patients were intubated throughout the study (n = 12), and half were extubated (n = 11) during the study.

Table 1 shows the mean IOP for both eyes in both intubated and extubated patients during dopamine infusion and after its cessation. The mean increase in IOP in extubated patients receiving dopamine was 22.9% (left eye) and 26.2% (right eye). The mean increase in IOP in intubated patients receiving dopamine was 44.7% (left eye) and 38.4% (right eye). There was no significant difference in IOP between left and right eyes when patients were either on or off dopamine. There were also no statistically significant differences in the IOP between intubated and extubated patients who were off dopamine. However, the IOP while receiving dopamine was significantly higher for both intubated and extubated patients when compared with baseline (off dopamine), and the mean increase (table 2) was significantly higher in intubated patients (41.9% increase) compared with extubated patients (24.2% increase).

Discussion

We have shown that critically ill patients receiving infusions of dopamine in the range of 1–3.75 $\mu g \cdot kg^{-1} \cdot min^{-1}$ have consistently and significantly higher IOPs than after discontinuation of dopamine. These elevations are similar to those observed previously with fenoldopam.[3]

Intraocular pressure is maintained by a balance between the formation of aqueous humor, passive filtration and active secretion of the ciliary process, and its drainage by outflow pathways, in particular the trabecular network and Schlemm's canal, into aqueous veins. Therefore, an increase in production or a decrease in drainage can lead to an increase in IOP, predisposing the retinal ganglion cells and optic nerve head to damage with a potential end result of blindness.

Table 2. Mean Intraocular Pressure (mmHg ± SEM)*

	Not Administered Dopamine	Administered Dopamine	Increase
Extubated (n = 11)	12.8 ± 0.6	16.0 ± 0.7	3.1 ± 0.6
Intubated (n = 12)	12.4 ± 0.6	17.6 ± 0.9	5.2 ± 0.9†

* Values are the mean of the left and right eyes combined. † $P < 0.05$ compared with mean increase in extubated patients.

Previous animal studies have shown that dopamine has no effect on IOP,[4] decreases IOP,[5] increases IOP,[6–8] or has a biphasic dose-dependent effect on IOP[9] depending on the species studied and the route of administration (*e.g.*, topical, intravenous, intravitreal).

There are two predominant subclasses of dopamine receptors. Dopamine-1 receptors are postsynaptic and are generally stimulatory, whereas dopamine-2 receptors act presysnaptically and are generally inhibitory.[10] Activation of these receptors elicits a variety of responses depending on their location throughout the body. Stimulation of peripheral dopamine receptors affects vascular tone, sodium homeostasis, and hormone secretion. Central dopamine receptor stimulation is involved in cognition, emotion, affect, locomotion, and neuroendocrine secretion. In the eye, stimulation of dopamine-2 receptors may lower IOP,[11,12] probably indirectly through mediation of sympathetic activity. Dopamine-1 receptors have been demonstrated to be present in the ciliary processes and body[13,14] and trabecular meshwork.[15] Activation causes stimulation of cyclic adenosine monophosphate[15,16] and changes aqueous humor dynamics,[1,8,17] either through increased production or decreased outflow (most likely) of aqueous humor. A recently released dopamine-1–specific agonist, fenoldopam, has been shown in human trials to increase IOP in both healthy patients[1–3] and in those with preexisting ocular hypertension.[18] Our study was designed to see if dopamine in doses believed to stimulate predominantly dopaminergic receptors would cause similar increases in IOP.

The clinical significance of these data are yet to be determined. In this observational study, there were many factors not controlled for that could have exerted some effect on IOP. We did not alter any therapy being provided, as we were not the primary physicians caring for these patients. Specifically, we did not control for the level of sedation, hemodynamic parameters, or other drug therapy (except as noted in Methods) that may have affected IOP. Sedatives and anesthetics generally

lower or have no effect on IOP.[19–24] Therefore, the increase in IOP observed while the patients were on dopamine could have been blunted from various sedative regimens. With regard to hemodynamic parameters, end-organ ischemia can be reduced through elevations in perfusion pressure, and certainly dopamine can be used to elevate blood pressure to improve tissue and organ perfusion. We tried to minimize this effect by selecting hemodynamically stable patients receiving low-dose dopamine (*i.e.*, $< 5\ \mu g \cdot kg^{-1} \cdot min^{-1}$), in whom there would be less effect on systemic blood pressure. Other studies have shown that dopaminergic stimulation alone without sympathetic stimulation can produce increases in IOP.[3,7,9] We did control for the well-documented diurnal variations in IOP[25] and for the presence of positive-pressure mechanical ventilation.

Our results raise additional issues. For instance, there was little variation in IOP from day to day until the dopamine was discontinued. While IOP in patients on dopamine was higher, the clinical significance of a 3–5-mmHg elevation in IOP in patients without preexisting ocular hypertension is probably minimal. There is a single case report implicating dopamine infusion with retinal infarction,[26] but this patient was on a dopamine infusion as high as $115\ \mu g \cdot kg^{-1} \cdot min^{-1}$; therefore, the possibility of overwhelming vasoconstriction from an α-adrenergic effect must be considered. A potential concern, however, is the possibility of an exaggerated response in patients with preexisting ocular hypertension. In a study by Everitt *et al.*[18] that examined the effects of fenoldopam in patients with preexisting ocular hypertension, five patients were withdrawn prematurely because their IOP exceeded the upper safe limit of the study (IOP $>$ 35 mmHg). Although fenoldopam is a more specific dopamine-1 receptor agonist, the possibility that dopamine may have a similar effect warrants further prospective evaluation.

The cause of the significantly greater increase in IOP observed in our patients being mechanically ventilated may be the result of impaired venous return secondary to positive intrathoracic pressure leading to impaired venous drainage. However, some studies have shown that neither short-term increases in positive end-expiratory pressure to 15 cm H_20 nor prolonged mechanical ventilation with positive end-expiratory pressure was shown to be correlated with IOP.[27]

In conclusion, we have shown that low-dose dopamine infusion is associated with consistently and significantly increased IOP in critically ill patients without preexisting ocular hypertension. This association should be considered by clinicians using low-dose dopamine therapy in critically ill patients. Although further study is needed to prospectively examine for ocular outcome, there may be potential risk in patients with preexisting ocular hypertension and in patients who might be unable to alert their caretakers to the symptoms of an ocular hypertensive crisis either because of sedation or mechanical ventilation.

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References

1. Piltz JR, Stone RA, Boike S, Everitt DE, Shusterman NH, Audet P, Zariffa N, Jorkasky DK: Fenoldopam, a selective dopamine-1 receptor agonist, raises intraocular pressure in males with normal intraocular pressure. J Ocul Pharmacol Ther 1998; 14:203–16

2. Elliott WJ, Karnezis TA, Silverman RA, Geanon J, Tripathi RC, Murphy MB: Intraocular pressure increases with fenoldopam, but not nitroprusside, in hypertensive humans. Clin Pharmacol Ther 1991; 49:285–93

3. Karnezis TA, Murphy MB, Weber RR, Nelson KS, Tripathi BJ, Tripathi RC: Effects of selective dopamine-1 receptor activation on intraocular pressure in man. Exp Eye Res 1988; 47:689–97

4. Elibol O, Guler C, Yuksel N: The effects of dopamine, haloperidol and bromocriptine on intraocular pressure. Int Ophthalmol 1992; 16:343–7

5. Shannon RP, Mead A, Sears ML: The effect of dopamine on the intraocular pressure and pupil of the rabbit eye. Invest Ophthalmol 1976; 15:371–80

6. Chiou GC, Chiou FY: Dopaminergic involvement in intraocular pressure in the rabbit eye. Ophthalmic Res 1983; 15:131–5

7. Potter DE, Rowland JM: Adrenergic drugs and intraocular pressure: Effects of selective beta-adrenergic agonists. Exp Eye Res 1978; 27:615–25

8. Virno M, Gazzaniga A, Taverniti L, Pecori Giraldi J, De Gregorio F: Dopamine, dopaminergic drugs and ocular hypertension. Int Ophthalmol 1992; 16:349–53

9. Hariton C: Biphasic dose-dependent effects of dopamine and involvement of dopamine autoreceptors on intra-ocular pressure in the rabbit. J Auton Pharmacol 1992; 12:335–47

10. Missale C, Nash SR, Robinson SW, Jaber M, Caron MG: Dopamine receptors: From structure to function. Physiol Rev 1998; 78:189–225

11. Mekki QA, Turner P: Stimulation of dopamine receptors (type 2) lowers human intraocular pressure. Br J Ophthalmol 1985; 69:909–10

12. Prunte C, Nuttli I, Markstein R, Kohler C: Effects of dopamine D-1 and D-2 receptors on intraocular pressure in conscious rabbits. J Neural Transm 1997; 104:111–23

13. Lograno MD, Daniele E, Govoni S: Biochemical and functional evidence for the presence of dopamine D1 receptors in the bovine ciliary body. Exp Eye Res 1990; 51:495–501

14. Mancino R, Cerulli L, Ricci A, Amenta F: Direct demonstration of dopamine D1-like receptor sites in the ciliary body of the rabbit eye by light microscopic autoradiography. Naunyn Schmiedebergs Arch Pharmacol 1992; 346:644–8

15. Karnezis TA, Tripathi BJ, Dawson G, Murphy MB, Tripathi RC: Effects of dopamine receptor activation on the level of cyclic AMP in the trabecular meshwork. Invest Ophthalmol Vis Sci 1989; 30:1090–4

16. De Vries GW, Mobasser A, Wheeler LA: Stimulation of endogenous cyclic AMP levels in ciliary body by SK&F 82526, a novel dopamine receptor agonist. Curr Eye Res 1986; 5:449–55

17. Virno M, Taverniti L, De Gregorio F, Sedran L, Longo F: Increase in aqueous humor production following D1 receptors activation by means of ibopamine. Int Ophthalmol 1996-97; 20:141–6

18. Everitt DE, Boike SC, Piltz-Seymour JR, VanCoevorden R, Audet P, Zariffa N, Jorkasky D: Effect of intravenous fenoldopam on intraocular pressure in ocular hypertension. J Clin Pharmacol 1997; 37:312–20

19. Al-Abrak MH, Samuel JR: Effects of general anaesthesia on the intraocular pressure in man: Comparison of tubocurarine and pancuronium in nitrous oxide and oxygen. Br J Ophthalmol 1974; 58:806–10

20. Carter K, Faberowski LK, Sherwood MB, Berman LS, McGorray S: A randomized trial of the effect of midazolam on intraocular pressure. J Glaucoma 1999; 8:204–7

21. Artru AA: Intraocular pressure in anaesthetized dogs given flumazenil with and without prior administration of midazolam. Can J Anaesth 1991; 38:408–14

22. Joshi C, Bruce DL: Thiopental and succinylcholine: Action on intraocular pressure. Anesth Analg 1975; 54:471–5

23. Mirakhur RK, Shepherd WF, Darrah WC: Propofol or thiopentone: Effects on intraocular pressure associated with induction of anaesthesia and tracheal intubation (facilitated with suxamethonium). Br J Anaesth 1987; 59:431–6

24. Presbitero JV, Ruiz RS, Rigor BM Sr, Drouilhet JH, Reilly EL: Intraocular pressure during enflurane and neurolept anesthesia in adult patients undergoing ophthalmic surgery. Anesth Analg 1980; 59:50–4

25. Shiose Y: Intraocular pressure: New perspectives. Surv Ophthalmol 1990; 34:413–35

26. Opremcak EM, Davidorf FH: Bilateral retinal infarction associated with high dose dopamine. Ann Ophthalmol 1985; 17:141–4

27. Teba L, Viti A, Banks DE, Fons A, Barbera M, Hshieh PB: Intraocular pressure during mechanical ventilation with different levels of positive end-expiratory pressure. Crit Care Med 1993; 21:867–70