Advance Publication

The Journal of Veterinary Medical Science

Accepted Date: 1 May 2012
J-STAGE Advance Published Date: 1 Lwp 2012
IOP change undergoing Anesthesia in Rhesus Macaques (Macaca mulatta) with Laser-induced Ocular Hypertension

RUNNING TITLE: IOP CHANGE ON ANESTHESIA IN MONKEYS

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Abstract

The objective of the study was to examine changes of intraocular pressure (IOP) undergoing anesthesia in Rhesus Macaques (*Macaca mulatta*) with Laser-induced Ocular Hypertension. Twenty male rhesus macaques (hypertensive glaucoma eye in OD; normal eye in OS) between 6 and 20 years of age were used for the study. The monkeys were anesthetized with ketamine hydrochloride (10mg/kg intramuscularly) and 1% isoflurane and then IOP in both eyes was measured by a single investigator using a calibrated Tonopen™ applanation tonometer (Mentor, Norwell, MA, U.S.A.). The mean IOP with ketamine anesthesia was 36.70 ± 12.04 (right eye: OD) and 15.88 ± 2.84 (left eye: OS). The mean IOP with isoflurane anesthesia was 19.98 ± 6.67 (right eye: OD) and 15.32 ± 2.15 (left eye: OS). Undergoing isoflurane anesthesia, the IOP of OD was significantly decreased. Conclusively, careful examination of IOP is required to prevent unexpected contraindication on glaucoma patient with isoflurane anesthesia.

**Key words:** anesthesia; glaucoma; intra ocular pressure; monkey
Aqueous humor secreted by the ciliary body flows through the pupil into the anterior chamber and exits the eye through a pathway comprised of trabecular meshwork [12, 2]. Intraocular pressure (IOP) is defined as the pressure of the volumes of intraocular, aqueous humor, choroidal blood, and vitreous humor. The volume of intraocular fluid depends on physiological changes of aqueous humor [2]. The IOP is variable in the dog but normally ranges from 14 to 25 mmHg. IOP can change depending on ocular conditions or diseases. Elevated IOP is the principle risk factor for the development of glaucoma. Glaucoma is one of the leading causes of blindness globally, and is characterized by an elevation in the internal fluid pressure of the eye resulting in the destruction of ocular structures and function [3, 5]. Because numerous ophthalmic procedures and anesthetic factors can affect IOP, careful examination of IOP is very important. In addition, various anesthetic agents may have both direct and indirect effects on IOP [4]. The effects are mediated by respiratory mechanisms and hemodynamic changes resulting from anesthesia [5]. Most anesthetics decrease IOP in proportion to the depth of anesthesia with the exception of ketamine [6]. It has been accepted that an increase in IOP influences the circulation in the optic system, which is considered the functional mechanism of vascular autoregulation in the region [10]. Autoregulation is the mechanism that adjusts the vascular resistance in changed perfusion pressures, so that intraocular blood flow remains constant [11]. This is necessary to stabilize tissue perfusion and capillary hydrostatic pressure. High IOP can lead to reduce perfusion pressure through the actions of autoregulation. IOP is significantly affected by changes in choroidal blood volume. Choroidal blood flow is autoregulated over a range of perfusion pressures to maintain normal IOP. The response of ocular regulation is impaired and disappears when IOP has been high for longer
periods of time [12]. This study was performed to measure IOP change while under ketamine and isoflurane as 2-type anesthesia using a rhesus macaque (*Macaca mulatta*) model with experimental laser-induced ocular hypertension.

All experiments were conducted in accordance with the Association for research in Vision and Ophthalmology (ARVO) Resolution for the Use of Animals in Ophthalmic and Vision Research. Twenty male rhesus macaques with the laser induced ocular hypertension between 6 and 20 years of age were used for the study. Ocular hypertension was produced in the right eyes (OD) of monkeys by repeated argon laser photocoagulation of the trabecular meshwork as previous studies [7, 9]. The monkeys were first anesthetized with ketamine hydrochloride (10mg/kg intramuscularly, Ketaset®, Fort Dodge, Madison, NJ, U.S.A.). Then, IOP in both eyes was measured by a single investigator using a calibrated Tonopen™ applanation tonometer (Mentor, Norwell, MA, U.S.A.). Secondly, the monkeys were anesthetized with 1% isoflurane (Isoflo®, Abbott Laboratories, Abbott Park, IL, U.S.A.) and 66% nitrous oxide. Then each animal was paralyzed with pancuronium bromide (0.05 mg/kg intravenously, Elkins-Sinn, Cherry Hill, NJ, U.S.A.) to reduce movement. After the animals were stable, IOPs in both eyes were measured with the same method and equipment as previously used. Before measuring IOP, topical anesthesia with 0.4% oxybuprocaine (Ciba Vision Ophthalmics, Duluth, GA, U.S.A.) was instilled in both eyes. Tonometry was performed three times in each eye and averaged for each measurement. The IOP was measured from 7 a.m. to 9 a.m (Fig. 1). Results are expressed as mean ± SD (standard deviation) and were analyzed by Student’s *t* test using SPSS (SPSS 12.0, SPSS Inc., Chicago, IL, USA). Statistical significance was defined as *p* < 0.05.

The mean IOP under ketamine anesthesia was 36.70 ± 12.04 (OD) and 15.88 ± 2.84
(OS). The mean IOP under isoflurane anesthesia was 19.98 ± 6.67 (OD) and 15.32 ± 2.15 (OS). Under ketamine anesthesia, IOP in the OD was always significantly higher than the IOP in the OS. However, after isoflurane anesthesia, only the IOP of OD induced ocular hypertension was significantly decreased (Fig 2). IOPs in the OS were not significantly changed before and after isoflurane anesthesia (Fig 3).

Control of IOP is most important during intraocular procedures. Moreover, the choice of anesthetics that influence IOP is the primary key to maintain ocular conditions. Several researchers have found that many general anesthetics are able to lower IOP in humans and animals. One study in rats demonstrated that anesthetics significantly reduce the measured IOP in both normal eyes and in those with experimental aqueous outflow obstructions [5]. On the other hand, it is reported that ketamine can elevate IOP by increasing the tone of the extraocular muscles [4]. In this study, IOP was not significantly changed by ketamine anesthesia. However, IOP was significantly decreased in the OD that induced ocular hypertension after isoflurane anesthesia. In this study, the experimental monkeys were anesthetized by a combined method with pancuronium, nitrous oxide, and isoflurane. Among the three agents, pancuronium has been used with widespread acceptance, because it is reported to have fewer cardiovascular side-effects. Pancuronium has the least impact on IOP, so it can be used during intraocular procedures [1]. When used for anesthesia, nitrous oxide is diluted in oxygen. It exerts a direct dose-dependent depressor effect on the myocardium. Isoflurane as an inhalation anesthetic has been studied and shown to induce a significant and sharp reduction in IOP [6]. Reduction in IOP continues slowly for the anesthetic period due to respiratory mechanisms, and as a result may possibly cause hemodynamic changes. This study just measured IOP alteration by anesthesia because of experimental
limitation. A further study related to physiologic changes may be required. Usually, depressants or anesthetics of the central nervous system decrease IOP in both eyes in proportion to the depth of anesthesia. However, in this study, decrease of IOP was only found in OD induced ocular hypertension, which was different from IOP at OS that remained normal. Any decrease in blood pressure by anesthesia may be transmitted directly to the eye, creating pressure on the aqueous vein, which drains the canal of Schlemm [11]. It means the blood flow autoregulation, and blood flow regulation has been studied and shown to be dependent on ocular perfusion pressure, as well as on the level of IOP itself [8, 11]. In this study, the autoregulation at OD might be destroyed by argon laser photocoagulation of the trabecular meshwork. Impaired autoregulation demonstrates important alternations in ocular blood flow. It is thought that severe changes in blood flow may induce the observed significant decrease of IOP at OD after isoflurane anesthesia. Conclusively, careful examination of IOP is required to prevent unexpected contraindication on glaucoma patient with isoflurane anesthesia.
ACKNOWLEDGMENTS

This work was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) grant funded by the Korean government (2009-0072677).

REFERENCES


Fig. 1. Experimental procedure to measure IOP undergoing anesthesia.
Fig. 2. Mean IOP in right eye (OD) based on two types anesthesia in monkey.

*Significantly different compared to ketamine as $p < 0.05$
Fig. 3. Mean IOP in left eye (OS) based on two types anesthesia in monkey.