



ESTONIAN UNIVERSITY OF LIFE SCIENCE
Institute of Veterinary Medicine and Animal Sciences

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**THE EFFECT OF TWO DIFFERENT PREOPERATIVE
ANESTHETIC REGIMENS ON INTRAOCULAR PRESSURE
IN DOGS**

KAHE ERINEVA PREOPERATIIVSE ANESTEETILISE REŽIIMI MÕJU
SILMA SISERÕHULE KOERTEL

Graduation Thesis in Veterinary Medicine
The Curriculum of Veterinary Medicine

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ABSTRACT

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<p>Sudden intraocular pressure (IOP) increase can have significant negative consequences in animals with corneal lesions or glaucoma and that is why it should be avoided whenever possible. IOP is defined by the pressure of intraocular aqueous humor on the eyes fibrous layer. The aim of the present study is to evaluate and compare the effect of methadone-dexmedetomidine-propofol (MDP) and methadone-midazolam-propofol (MMP) on IOP in dogs before general anesthesia with isoflurane. Also to evaluate the IOP rise after endotracheal intubation. The study population was 12 adult dogs of different breeds obtained from the University of Life Sciences Small-Animal Clinic who were going to undergo orthopedic knee surgery. The dogs were otherwise clinically healthy. Pre-anesthetic physical examination was done and blood work consisting of blood urea nitrogen (BUN) and blood creatinine (CREA) in all cases. Before entering the study, all subjects went through an ophthalmological examination. Statistical analyses were performed and all the figures were constructed with program R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria). When comparing the groups MDP and MMP the author concludes that a better anesthetic regimen for ophthalmological procedures is first one because the IOP remains relatively consistent throughout the preoperative period and there are not any acute rises in IOP. All the results gotten from this study should be interpreted with caution because of the small study population. A larger study population is needed to make final conclusions.</p>			
Keywords: ophthalmology, methadone, midazolam, propofol, dexmedetomidine			

LÜHIKOKKUVÕTE

Eesti Maaülikool Fr. R. Kreutzwaldi 1, Tartu 51006		Lõputöö lühikokkuvõte	
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<p>Äkiline silmasisese rõhu (ingl k <i>intraocular pressure – IOP</i>) suurenemine võib põhjustada märkimisväärseid negatiivseid tagajärgi sarvkesta kahjustustega või glaukoomiga loomadel, mistõttu tuleks seda võimalusel vältida. IOP määrab silmasisese vesivedeliku rõhk silmamuna fibrooskihile. Käesoleva lõputöö eesmärk on hinnata ja võrrelda gruppide metadoon-deksmedetomidin-propofool (ingl k <i>methadone-dexmedetomidine-propofol – MDP</i>) ja metadoon-midasolaam-propofool (ingl k <i>methadone-midazolam-propofol – MMP</i>) mõju IOP-le koertel enne üldanesteesiat isofluraaniga. Samuti hinnata IOP tõusu pärast endotrahheaalset intubatsiooni. Uuringupopulatsiooniks oli 12 erinevat tõugu täiskasvanud koera, kes läksid plaanilisele ortopeedilisele põlveoperatsioonile Eesti Maaülikooli väikelooma kliinikus. Kõik loomad olid üleüldiselt kliiniliselt terved. Igale loomale tehti anesteesiaeelne kliiniline ülevaatus ja vereanalüüs, mis koosnes vere urea lämmastikust (ingl k <i>blood urea nitrogen – BUN</i>) ja kreatiniinist (ingl k <i>creatinine – CREA</i>). Kõik loomad läbisid oftalmoloogilise ülevaatus. Statistilised analüüsid ja joonised koostati programmiga R versiooniga 3.5.3 (R Foundation for Statistics Computing, Viin, Austria). MDP ja MMP gruppide võrdlemisel leidis autor, et parem preoperatiivne anesteetiline režiim oftalmoloogilisteks protseduurideks on MDP grupp, sest IOP jääb preoperatiivse perioodi ajal suhteliselt stabiilseks ja puudub äge IOP tõus. Käesoleva uuringu tulemusi tuleb väikese uuringupopulatsiooni tõttu käsitleda ettevaatlikult. Lõplike järelduste tegemiseks on vaja suuremat uuringupopulatsiooni.</p>			
Märksõnad: oftalmoloogia, metadoon, midasolaam, propofool, deksmedetomidin			

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LIST OF ABBREVIATIONS

AAP – angular aqueous plexus
AH – aqueous humor
ARC – arcuate nucleus
ASA – American Society of Anesthesiologists
ATPase – adenosine triphosphatase
BCS – Body Condition Score
BUN – blood urea nitrogen
BW – body weight
CB – ciliary body
CREA – creatinine
CSTM – corneoscleral trabecular meshwork
GABA – gamma-aminobutyric acid
ICA – iridocorneal angle
IM – intramuscular
IOP – intraocular pressure
ISVP – intrascleral venous plexus
IV – intravenous
JCT – juxtacanalicular connective tissue
MDP – methadone-dexmedetomidine-propofol
MMP – methadone-midazolam-propofol
NMDA – N-methyl-d-aspartate
NO – nitric oxide
NPE – nonpigmented epithelium
PE – pigmented epithelium
PL – pectinate ligament
RCC – radial collector channels
SQ – subcutaneous
TM – trabecular meshwork
USO – uveoscleral outflow
USTM – uveoscleral trabecular meshwork
UTM – uveal trabecular meshwork

INTRODUCTION

Anesthesia is a very important part of veterinary ophthalmic surgery. Intraocular pressure (IOP) is defined by the pressure of intraocular aqueous humor on the eye's fibrous layer. This pressure is determined by volumes of various components such as blood inside the vessels of the eye and aqueous humor (AH). Many drugs used in anesthesia can cause changes in ocular AH formation and blood flow and therefore the IOP. When preoperative changes on IOP happen they can cause such dramatic consequences as vitreous or lens prolapse when the globe is opened during intraocular surgery, also rupture of the eye, expulsive choroidal hemorrhage or retinal detachment. This is why the correct selection of anesthetic drugs must be made to maintain normal IOP (Tamura et al, 2002).

In this thesis work, the author describes the anatomy of the eye, functional anatomy of the AH outflow facilities, rebound tonometry and the factors that affect it. Author of this thesis chose four different drugs used in anesthesia that affect the IOP. In recent years there has been a lot more information published regarding the effects of preanesthetic and anesthetic drugs on IOP in dogs, but still, there is very little information about the effect of methadone on IOP. Also there is little recent information about how midazolam affects the IOP. This is also why the author of this thesis chose these two drugs used in anesthesia among with drugs that are more researched like dexmedetomidine and propofol.

The aim of the present study is to evaluate and compare the effect of methadone-dexmedetomidine-propofol (MDP) and methadone-midazolam-propofol (MMP) on IOP in dogs before general anesthesia with isoflurane. Also to evaluate the IOP rise after endotracheal intubation. The evaluation and comparison were done using statistical analysis using the Tukey *post-hoc* test to perform a pairwise comparison of the groups and the time moments. The relationships between dog's age, weight, blood urea nitrogen (BUN) and creatine (CREA) concentrations and IOP measured at different time moments were studied with linear correlation analysis. Statistical analyses were performed and all the figures were constructed with program R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria).

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1. LITERATURE REVIEW

1.1. Anatomy and physiology of the eye

The visual organ also is known as the eye (in Latin *organum visus, seu oculus*; in Greek *ophthalmos*) is one of the most important information collectors. The eyeball is located in the eye socket and is almost round, the smaller anterior segment comparing to the bigger posterior part has a shorter radius of curvature. The anterior segment is filled with AH (Ernits & Nahkur, 2017). The posterior segment is filled with vitreous. The lens divides the eye into the anterior and posterior segments (Akers & Denbow, 2013). The average diameter of an eyeball is usually between two to two and a half centimeters in dogs. The eyeball consists of three layers that cover each other. Starting from the outside these layers are the fibrous, vascular and the inner layer of the eyeball also known as the retina. The fibrous layer of the eyeball is a strong connective tissue, that composes of an anterior cornea and posterior sclera that surrounds the eyeball (Figure 1). The fibrous layer protects eyeball mechanically and contributes to the formation of IOP (Ernits & Nahkur, 2017).

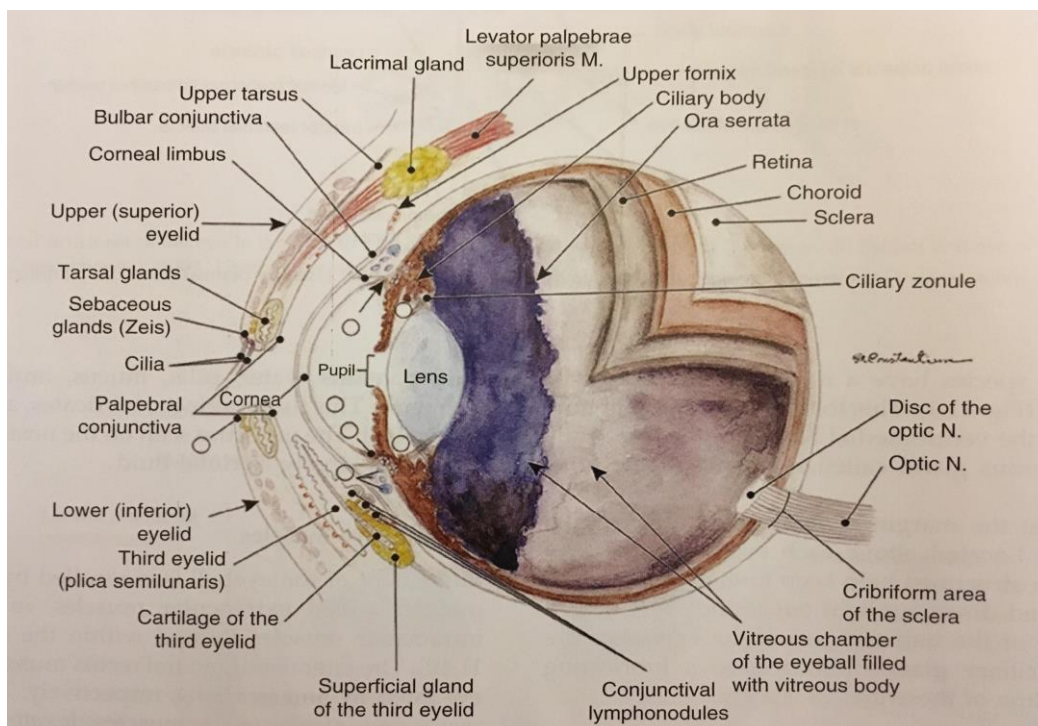


Figure 1. Median section of the eye of a dog. Muscle (M); nerve (N) (Akers & Denbow, 2013).

The cornea is with a smaller diameter than the sclera. It is curved outside and transparent. There are no blood and lymph vessels in the cornea, therefore its nutrition is carried out through tear fluid and eyeball anterior chamber AH. Sclera compared to the cornea is more extensive and opaque. The sclera is composed of white collagen fibers and is the skeleton of the eyeball. Sclera also contains elastic fibers and some blood vessels, but no lymph vessels. Eyeball muscles are attached to the outer surface of the sclera (Ernits & Nahkur, 2017).

The vascular layer of the eyeball is divided into the posterior choroid, in the middle, there are the ciliary body (CB) and anterior iris (Figure 1). The choroid gives nutrients to the retina and regulates IOP. The choroid is highly vascularized and pigmented. There are four big vorticoses veins that come to the choroid through the sclera. If the vein openings narrow it causes the increase of IOP and development of glaucoma. The CB is a continuation of the choroid and it surrounds the lens, it also includes ciliary muscle which helps the lens to adapt to the distance of the subject being examined. The retina is also involved in the formation of the CB (Ernits & Nahkur, 2017). AH is secreted by CB nonpigmented epithelium (NPE) through three basic mechanisms that are ultrafiltration, diffusion and active secretion (Maggo, 2015).

The iris is a diaphragm to light that widens or shrinks the pupil depending on the intensity of light irritation. The pupil shrinks due to the parasympathetic innervation of the iris sphincter muscle and it happens because of strong light irritation when looking at objects close by, during sleeping and at the beginning of the third phase of anesthesia. The pupil widens due to the sympathetic innervation of the iris dilator muscle in absence of light irritation, fear, anger and usually when the animal is in deep anesthesia. There is a lot of pigment and blood vessels. The inner layer of the eyeball forms the retina (Figure 1) (Ernits & Nahkur, 2017).

1.1.1. Functional anatomy of the aqueous humor outflow facilities

AH is the fluid that fills the posterior and anterior chambers of the eyeball (Pizzirani & Kong, 2015). The AH composes of water, electrolytes, glucose and amino acids (Ernits & Nahkur, 2017). Main roles of the AH is to provide nutrients and also metabolic removal of

waste from the parts of the ocular structures that are avascular and also contributing in maintaining of the IOP without changing the refractive status of the eye. The fluid dynamics and its composition associated with its flow are voluble and undergo changes associated with disease and age. Particular importance is the resistance to the outflow of AH from the anterior chamber, which is influenced by physiologic, morphologic and biochemical dynamic factors. Also, AH is important because its solutes participate in establishing the anterior chamber immune deviation by carrying and distributing different molecules, like proteins, that direct and promote remodeling and changes in the anterior segment that are associated with both disease and age. There are three major specific aspects of the aqueous that need to be considered: 1) aqueous production, 2) composition, and 3) outflow (Pizzirani & Kong, 2015).

IOP physiologic range is maintained through the constant balance between AH production and aqueous outflow. The pressure gradient within the eye has to be between specific values but may vary individually in different daily patterns and with aging. Mean normal values for IOP in dogs are 12...25 millimeter of mercury (mmHg), however, most dogs have normal pressure under 20 mmHg. IOP values may vary depending on the technique of measurement and time (Pizzirani & Kong, 2015). IOP varies during the day with circadian phases that drop and peaks at different times of the day. In dogs, the highest peak in IOP was measured in the morning and IOP is lower in the evening time (Giannetto et al, 2009). Baseline IOP in dogs decreases with the increase of age. Although it seems that outflow of aqueous decreases with age, the production of AH also decreases (Pizzirani & Kong, 2015).

1.1.1.1. Aqueous production and composition

There are two mechanisms, passive and active, that are responsible for aqueous production and contribute to its composition. Both passive mechanisms, ultrafiltration and passive diffusion of plasma occur in the CB stroma that is vascularized. The passive mechanisms do not contribute very much to the formation of AH. Ciliary blood vessels endothelium is fenestrated and that is why diffusion of solutes travel according to a concentration gradient maintaining the balance between tissues and compartments. The substances that have high lipid solubility coefficients can freely move across cellular membranes (Maggo, 2015; Pizzirani & Kong, 2015).

Ultrafiltration lets the molecules move across a cell membrane following an osmotic gradient or a hydrostatic force and it results because of the differences between the IOP and pressure of the CB capillaries and differences in their solute concentration. In the CB capillaries, the hydrostatic pressure has been estimated to be between 25...33 mmHg, whereas the vascular protein oncotic pressure is about 14 mmHg. Lower oncotic and higher hydrostatic forces would both favor resorption of AH. If the IOP value would be around 15 mmHg, it can be understood how much higher the hydrostatic pressure would have to be to achieve the relevant amount of aqueous formation through this passive mechanism (Pizzirani & Kong, 2015). Passive mechanisms within the CB are able to generate a reservoir fluid. Because there is no true epithelium on the anterior surface of the iris diffusion and leakage of diluted plasma occurs from the ciliary vessels into the anterior chamber (Pizzirani & Kong, 2015).

It is thought to be that the AH is formed by active transport of bicarbonate, chloride and sodium ions from the stroma into the posterior chamber at the same time passive movement of water in the same direction takes place. AH flows through the pupil to the anterior from the posterior chamber because there is a pressure gradient established by the active process of AH formation in the posterior chamber (Klein, 2013; Pizzirani & Kong, 2015).

Active mechanisms account for 80%...90% of AH formation. Energy is required for active secretion of AH which is provided by hydrolysis of the adenine triphosphate and relies basically on two enzymes: a carbonic anhydrase and an adenosine triphosphatase (ATPase) sodium/potassium (Na/K) pump. The structural site for active secretion is based in the NPE of the ciliary processes where the two enzymes are highly concentrated (Pizzirani & Kong, 2015). Carbonic anhydrase accounts for about 40%...50% of the aqueous production (Maggo, 2015). More than 70% of the aqueous production is because of the active formation through an ATPase Na/K pump. Other solutes, like chloride, are increased through secondary active transport mechanisms (Pizzirani & Kong, 2015).

The two active mechanisms described share some of the pathways. Sodium and bicarbonate active release into the posterior chamber is mediated by these enzymes, then the osmotic gradient is made and the ultrafiltrate of plasma can move from the stroma of the CB into the posterior chamber (Figure 2). The system is sensitive to the IOP level and decreases when IOP increases (Pizzirani & Kong, 2015).

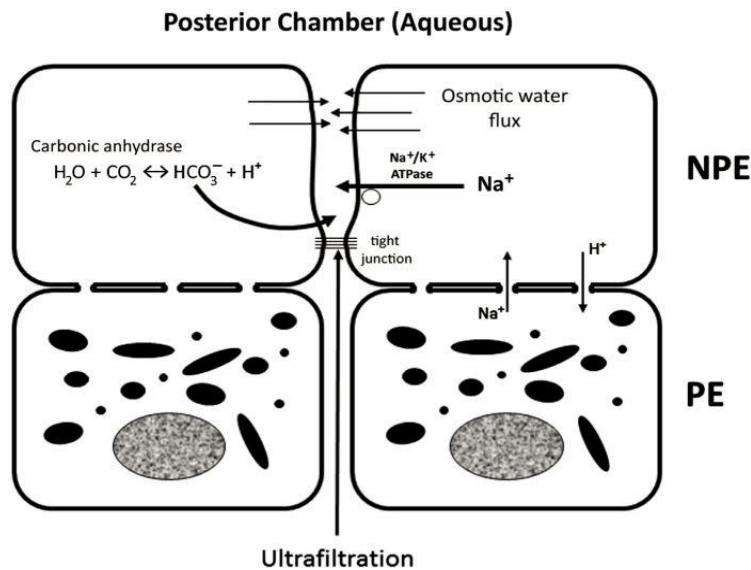


Figure 2. Mechanisms of aqueous humor formation. Sodium (Na^+) and bicarbonate (HCO_3^-) active movement increases the solute concentrations in the posterior chamber on the proximity of the ciliary processes and a positive osmotic gradient is created that revokes the fluids collected in the ciliary tissues because of diffusion and ultrafiltration. Adenosine triphosphatase (ATPase); nonpigmented epithelium (NPE); pigmented epithelium (PE) (Pizzirani & Kong, 2015).

1.1.1.2. Pathways of aqueous humor outflow

The outflow pathways are a complex hydraulic system that allows constant AH exit from the eyeball, but still maintains a physiologic IOP balanced with aqueous secretion. IOP increases when the regulation of the AH outflow is impaired. The outflow does not involve any active transport mechanisms. There are two main different outflow pathways that are usually considered most important to IOP balance. These are the anterior/trabecular or conventional outflow and the posterior or unconventional or the uveoscleral outflow (USO). In case of conventional outflow, AH flows through the trabecular meshwork (TM) as bulk flow derived by the pressure gradient, that is higher in the eyeball when compared with the distal outflow vessels (Maggo, 2015; Pizzirani & Kong, 2015).

The anatomical site of the conventional outflow is the iridocorneal angle (ICA), where the pectinate ligament (PL) slender strands connect the base of iris to the inner peripheral cornea. The ICA is comprised of two TM, the cobweblike uveal trabecular meshwork (UTM) and the lamellated corneoscleral trabecular meshwork (CSTM) which also includes uveoscleral trabecular meshwork (USTM). There is one more section listed that is a part of the TM which is the nonlamellated cribriform region or juxtacanalicular tissue (JCT). The

AH flows through the PL into the TM and from there it goes into the aqueous angular plexus and the episcleral veins (Figure 3) (Samuelson & Streit, 2012; Maggo, 2015, Pizzirani & Kong, 2015).

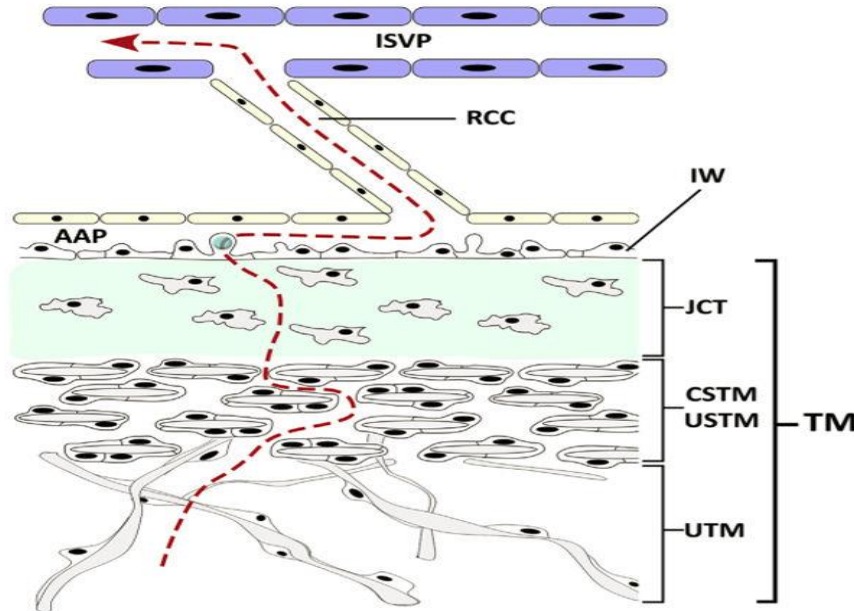


Figure 3. Aqueous outflow. Aqueous (red dotted line) movement through the trabecular meshwork (TM) outflow pathway from the ciliary cleft through the trabecular beams of the uveal TM (UTM), the corneoscleral or uveoscleral TM (CSTM/USTM) and the extracellular matrix of the juxtacanalicular connective tissue (JCT). The fluid goes through the inner wall (IW) endothelial cells by the formation of intracellular giant vacuoles that open into the angular aqueous plexus (AAP) lumen. With large radial collector channels (RCC) the AAP is connected leading to the intrascleral venous plexus (ISVP) (Pizzirani & Kong, 2015).

In the case of unconventional outflow, it is greatly independent of the IOP and regulated mostly by osmotic and hydrostatic gradients. The USO allows the drainage of AH posteriorly along with the supraciliary-suprachoroidal spaces and into the sclera close by. This pathway only accounts for 15% of the total AH drainage in dogs and it is influenced by the CB muscle contraction and the difference in hydrostatic pressure between the suprachoroidal spaces and the anterior chamber (Maggo, 2015; Pizzirani & Kong, 2015; Johnson et al, 2017).

1.2. Drugs used in anesthesia that affect the intraocular pressure

1.2.1. The mechanism of intraocular pressure change by drugs used in anesthesia

Sudden IOP increase can have significant negative consequences for animals with corneal lesions or glaucoma and that is why it should be avoided whenever possible. When there is a sharp rise in IOP it can cause damage to the optic nerve, globe rupture or prolapse of the ocular contents in cases of scleral or corneal instability. Animals that are undergoing surgery due to their ocular disease or even unrelated procedures could have a clinically significant impact on IOP and that should be considered (Smith et al, 2018).

Costa et al (2015) say that anesthetic drugs can alter the IOP by three different mechanisms either: 1) directly by inducing changes in the intraocular blood volume or aqueous, 2) locally by changing the tone of extraocular muscles which alters the sclera external compression or 3) indirectly by changing the vascular tone or the central control of ocular pressure.

1.2.2. Methadone and other opioids

1.2.2.1. Methadone and other opioids introduction

Methadone is an opioid analgesic used both in veterinary and human medicine primarily for analgesic purposes and in addition it is used for sedation in dogs. Methadone is a full synthetic μ -opioid receptor agonist, an antagonist on N-methyl-d-aspartate (NMDA) receptors and acts as a serotonin and norepinephrine reuptake inhibitor (Elwell-Cuddy et al, 2017). The action of methadone is to bind to κ -opioid and μ -opioid receptors on nerves and inhibit neurotransmitters release that is involved with the transmission of pain stimuli (for example substance P) (Papich, 2016). The fact that methadone has NMDA antagonistic effect makes it useful in the management of central sensitization and chronic pain syndromes (Yamaoka & Auckburally, 2014). The average plasma protein binding percentage is 64,8% in dogs. Methadone pharmacokinetics can be variable and dogs have shown side effects of overexposure like respiratory depression, sedation and cardiac arrhythmias which could be the combination of high doses and/or slow metabolism (Elwell-Cuddy et al, 2017).

The side effects of methadone are unavoidable and predictable. However, in dogs dysphoria and excitement which are seen in other opioids have not been as common with methadone. The side effects may include vomiting, miosis of the eye, urinary retention, constipation, sedation and bradycardia (Papich, 2016). Although methadone usually does not cause emesis. It is explained by its good lipid solubility and because of that, it crosses the brain barrier to give anti-emetic effects in the vomiting center. This can be helpful in cases where vomiting is undesirable for example increased intracranial pressure or IOP (Yamaoka & Auckburally, 2014). In dogs, panting may occur as a result of thermoregulation changes (Papich, 2016).

Methadone is indicated for sedation, short-term analgesia and adjunct to anesthesia. The drug is compatible with most of the anesthetic drugs and can be used as part of a multimodal approach to anesthesia and analgesia (Papich, 2016). Methadone can be given by intramuscular (IM), subcutaneous (SQ) or intravenous (IV) administration (Yamaoka & Auckburally, 2014). The usual dose for dogs is 0,1...0,5 milligrams per kilogram (mg/kg) of body weight (BW) IV or 0,5...2,2 mg/kg SQ or IM with the interval 3...4 hours. The half-life of methadone in dogs is 2...4 hours with the clearance of 30 milliliters per kilogram per minute (ml/kg/min) (Papich, 2016).

1.2.2.2. Methadone and other opioids effect on intraocular pressure

There is little research done on methadone and how it changes IOP in small animals. Morphine causes ocular hypotension and miosis and through that decrease in IOP. Because methadone is similar to morphine in the mechanism of action the effect on IOP can be predicted (Dortch-Carnes & Russell, 2006). Opioids also cause respiratory depression which increases the arterial partial pressure of carbon dioxide and that results in an increase of IOP, because carbon dioxide causes vasodilatation and through that could increase choroidal blood volume (Rauser et al, 2012). When morphine is systemically administrated pupillary constriction occurs because there is direct excitation of the oculomotor nuclear complex. When nerve cell bodies in the oculomotor nuclear cortex are stimulated increase of the parasympathetic output happens to the iris and results in miosis (Stephan et al, 2003).

Methadone, like other opioids, may cause ocular hypotension, miosis of the pupil causing lowering of the IOP (Dortch-Carnes & Russell, 2006). Results from Dortch-Carnes and Russell (2016) study indicate that morphine-induced reduction in pupil diameter and ocular hypotension are opioid-receptor-mediated responses that are linked to the release of nitric oxide (NO). The μ_3 opioid receptor subtype has a NO-releasing activity and is sensitive to inactivation by glutathione and that is why it is concluded that morphine-induced miosis and ocular hypotension are mediated partly by activation of the μ_3 opioid receptor.

An opioid peptide neuron/humoral feedback regulation may be involved in IOP changes. There is major endogenous opioid peptide in the brain called bendorphin. In the hypothalamic arcuate nucleus (ARC) originates the β -endorphin neuron. It seems, therefore, possible that opioid neurons originating in the ARC might be involved in central bilateral regulation of IOP (Jin et al, 2014). Dortch-Carnes & Russell (2006) state that opioids bind to the same site as those that are used by endogenous opioid peptides. Activation of these brain opioid receptors has shown to have effects on iris function and IOP.

1.2.3. Dexmedetomidine

1.2.3.1. Dexmedetomidine introduction

Dexmedetomidine is pharmacologically active D-isomer of the racemic compound called medetomidine and it is a highly selective agonist at the α_2 -adrenoreceptors. Alpha₂-agonist decreases the release of neurotransmitters from the neuron by binding to presynaptic alpha₂ receptors (negative feedback receptors). The result is decreased sympathetic outflow and therefore sedation and analgesia this is also why dexmedetomidine is used on dogs. Peak effect of the drug is observed 15 minutes after administration (Artigas et al, 2012; Rauser, 2012; Papich, 2016).

The most common acute side effect in dogs is vomiting. It is recommended to withhold food for several hours to minimize emesis (Papich, 2016). The hemodynamic effects of dexmedetomidine are characterized by biphasic blood pressure response, increases systemic vascular resistance, decreases heart rate and increases central venous pressure

(Rauser, 2012). The responses to α_2 receptors activation in other areas include decreased salivation, decreased bowel motility in the gastrointestinal tract, decreased secretion, contraction of vascular and other smooth muscles, inhibition of renin release, increased glomerular filtration and increased secretion of sodium and water in the kidneys, decreased IOP and decreased insulin release from the pancreas (Gertler et al, 2001).

Dexmedetomidine can be used together with other anesthetics such as ketamine, propofol, thiopental, benzodiazepines, and inhalant gas anesthetics and also among with analgesics such as opiates but lower doses of other drugs are needed when used with dexmedetomidine. It can be used IV or IM (Papich, 2016). The IV dose for dexmedetomidine is 0,5...6 micrograms per kilogram (mcg/kg) (Weerink et al, 2017).

1.2.3.2. Dexmedetomidine effect on intraocular pressure

In the study done by Artigas et al (2012) where they researched the effects of IV administration of dexmedetomidine on IOP and pupil size in clinically normal dogs, they found that dexmedetomidine reduced the IOP after 20 minutes of IV administration. They also say that α_2 -agonist reduce IOP. It is proposed that there are three mechanisms that explain the α_2 -adrenergic modulation of IOP. Prejunctional α_2 -receptors activation causes the inhibition of norepinephrine release, and therefore reducing a stimulus for aqueous production. But at the same time, the activation of postjunctional vascular α_2 -receptors causes ciliary vasoconstriction and decreases ciliary blood flow. Lastly, postjunctional epithelial α_2 -receptors activation inhibits adenylate cyclase. Also, the corneal application of α_2 -agonists decreases ciliary oxygen tension, aqueous production, ciliary blood flow, episcleral venous pressure and therefore decreases the IOP. Rauser et al (2012) say that IOP can also be altered by the rigidity of the sclera, by the tone of extraocular muscles and by external pressure on the globe, eyelid or extraocular muscles.

The tone of the intraocular vasculature, arterial inflow, and venous outflow determine the intraocular blood volume. IOP is modified by there variations in intraocular blood volume. When administered intravenously dexmedetomidine it produces a transitory increase in blood arterial pressure. In the first 5...10 minutes of sedation, this effect appears and after that systemic arterial pressure lessens. IOP can be modified during the period when the

transient increase in systemic blood pressure occurs. Also, a relationship exists between IOP and central venous pressure. Central venous pressure increase can increase IOP and choroidal blood volume, impairing the AH drainage into the venous system. Although choroidal blood flow autoregulation minimizes these effects in the IOP (Artigas et al, 2012).

They also say that the study concluded in human patients that went under intraocular surgery and were sedated with dexmedetomidine the reduction in IOP was explained only by the indirect hemodynamic effect. Whilst moderate decrease in blood pressure has little effect on IOP this study established that IOP value reduces when the mean arterial pressure diminishes below 90 mmHg (Artigas et al, 2012; Rauser et al, 2012). A study done by Rauser et al (2012) showed that when IV administration of medetomidine or dexmedetomidine in combination with butorphanol was given to dogs it caused a transient increase and subsequent decrease of IOP relative to baseline. Smith et al (2018) conducted a study where they used dexmedetomidine/hydromorphone as premedication and found that sedation with hydromorphone and dexmedetomidine significantly decreased IOP in clinically healthy dogs.

1.2.4. Propofol

1.2.4.1. Propofol introduction

Propofol is a hypnotic alkyl phenol, nonbarbiturate, short-acting (about 10 minutes), nonsteroid that is associated with rapid smooth induction and rapid recovery (Hofmeister et al, 2008; Hasiuk et al, 2014; Webb et al, 2018). The action mechanism on the central nervous system is quite complex with interactions at various neurotransmitter receptors (Chidambaran et al 2015). Propofol causes depression of the central nervous system through its effect on the gamma-aminobutyric acid (GABA) receptor. Propofol decreases GABA from dissociating from its receptors and through that increasing chloride conductance through channels, inhibiting the postsynaptic neurons and hyperpolarizing of the postsynaptic cell membranes. This produces the induction of anesthesia in an animal (Papich, 2016).

The most common adverse effect is respiratory depression and apnea, which more likely happen when the dose is increased. Dose-dependent cardiovascular depression can happen, but the severity of cardiac side effects is usually low. Also, propofol can induce vasodilatation, which can be minimized by giving IV fluids. Other adverse effects are decrease in IOP, spontaneous muscle movements (muscle rigidity, paddling, tremors), panting, salivation, nystagmus, and retraction of the tongue (incidence 3%...7%). Less frequent side effects include emesis during the recovery period and pain. Injection pain is more likely to happen in humans than in dogs. The pain is caused by the free propofol in the formulation. Hypoxia, apnea, and cyanosis may happen upon induction (Papich, 2016).

Propofol can be safely used with several other anesthetics and adjuncts. It has been used together with glycopyrrolate, acepromazine, atropine, xylazine, halotane, oxymorphone, and isoflurane without any interactions noticed. Sole propofol dose for dogs is 6,6 mg/kg IV slowly over 30...60 seconds. If it is necessary, an additional dose can be administered at 0,5...1 mg/kg IV for intubation. If the animal is premedicated with α_2 -agonist (for example dexmedetomidine) or other premedications the dose should be lowered by 20%...30%. After intubation maintenance dose can be used 1...3 mg/kg every 2...5 minutes (Papich, 2016; Plumb, 2011).

1.2.4.2. Propofol effect on intraocular pressure

A study done by Costa et al (2015) suggests that propofol can safely be used for intraocular surgery because it significantly reduces the IOP and that anesthesia induction with propofol would be especially recommended for a dog with tear deficiencies because propofol did not reduce tear production. The study showed that propofol caused a transient post-induction non-significant IOP rise, followed by a significant reduction. It remains unclear why this transient elevation of IOP happens, but some authors postulate that it happens because of drug effect on the central nervous system which alters the production and outflow of AH. Webb et al (2018) add that 2...4 minutes after propofol is given the rise on IOP is the highest.

A study done by Hasiuk et al (2014) showed that IV administration of propofol caused an increase in IOP. Costa et al (2015) say that the difference could be explained by the fact

that some studies give propofol, then intubate the patient, measure the IOP and then stop IOP measurements right after orotracheal intubation which causes the rise in IOP that was seen. This is also the case with Hofmeister et al (2008), Gunderson et al (2013) and Hasiuk et al (2014) studies. They measured IOP when jaw tone was absent after propofol was given and right after intubation. Webb et al (2018) study also showed an increase in the IOP, but again IOP was measured when the jaw tone was absent after propofol induction. The study conducted by Costa et al (2015) measured the IOP also 30 minutes after propofol administration so there is a reason to believe that propofol causes IOP decrease in the long perspective.

1.2.5. Midazolam

1.2.5.1. Midazolam introduction

Midazolam is a chemically synthesized water-soluble imidazobenzodiazepine derivative and has pharmacological effects such as anesthetic, hypnotic, sedative, strong anticonvulsive effect, and anxiolytic effects (Papich, 2016; Hamano et al, 2018). It is central-acting central nervous system depressant that binds to a specific GABA-binding site. Midazolam may modify the GABA-binding sites and increase the action of GABA on nerve cells. Sedative effects of midazolam may be attributed to potentiation of GABA pathways which act to regulate the monoamine neurotransmitters release in the central nervous system (Papich, 2016). Midazolam intensifies the activation of γ -aminobutyric acid, a major inhibitory neurotransmitter of the brain and that causes the patient to be calm (Tamura et al, 2002). The peak of midazolam in plasma from IM injection is 7...8 minutes (Papich, 2016).

The adverse effects of midazolam IV administration can be serious cardiorespiratory depression. Some dogs may get paradoxical excitement. Midazolam should be given cautiously when administered IV with opioids. Midazolam can be used safely with several sedatives, preanesthetics, sedatives, and anticonvulsants but because midazolam is metabolized in the liver by P450 enzymes which may be inhibited by some drugs like ketoconazole and omeprazole so they will inhibit the clearance of midazolam in dogs. The dose of midazolam for dogs is 0,1...0,4 mg/kg IV or IM (Papich, 2016; Plumb, 2011).

1.2.5.2. Midazolam effect on intraocular pressure

Gunderson et al (2013) study found that there was no substantial increase in IOP in clinically healthy dogs after getting a ketamin-midazolam combination. Midazolam is a muscle relaxant that also lowers the extraocular muscle tone. The authors of the study also say that they cannot rule out the effects of any interactions between midazolam and the other anesthetic induction drugs themselves on IOP and pupillary diameter. Ghaffari et al (2010) say that ketamine-midazolam combination had no clinically important effect on the IOP.

More studies have been done with midazolam and its effect on IOP, but the studies are outdated. A study conducted by Artru (1991) says that midazolam is a good drug to use to control IOP. Tamura et al (2002) study showed that a combination of xylazine and ketamine was found to increase IOP but the subsequent administration of midazolam reduced IOP in dogs.

1.3. Tonometry and the factors that influence it

1.3.1. Rebound tonometry

IOP is usually measured indirectly (noninvasive) by tonometry and in this thesis, the rebound tonometry was used. The device used is to date the only hand-held tonometer, the TonoVet (Icare Oy), that is calibrated for veterinary species, including dogs. A study that evaluated three hand-held tonometers in normal canine eyes says that TonoVet is the most accurate tonometer (Tofflemire et al, 2017). Cervino (2006) says that rebound tonometry is a good device due to its relatively low cost, portability and the fact that there is no need for analgesia or anesthesia.

The method of rebound tonometry establishes the IOP using the rebound kinematics of a light metallic probe that is being propelled against the corneal surface electromagnetically. The disposable rod probe consists of a magnetized steel wire shaft that is covered in one end with a round plastic tip that minimizes the risk of injury to the cornea when the probe touches the cornea. After the measurement button is pressed the probe hits the eye and then

bounces back. The bouncing movement is detected by a solenoid inside the tonometer. The magnet starts to move and induces a voltage into the solenoid. The probe motion parameters are monitored. As the IOP increases the probe bounces faster and consequently, the higher the IOP, the shorter is the impact duration. The tonometer software is programmed so that six measurements are taken, but discards the highest and lowest readings of IOP and calculates the mean IOP value from the remaining measurements (Cervino, 2006; Von Spiessen et al, 2015).

As the iCare, TonoVet User's Guide and Maintenance Manual (2014) states the tonometer has to be in a horizontal position during the measurement and the distance should be 4...8 millimeters (mm) from the probe to the cornea to get an accurate reading. It is very important that the tip of the probe needs to contact the central cornea because the result varies in different parts of the eye.

1.3.2. Factors that influence tonometry

Rebound tonometry is affected by corneal characteristics such as elasticity and thickness. IOP should not be measured from the cornea that is abnormal or damaged. Rebound tonometry is good because the probe tip is small and measurements can be taken from areas of the cornea that are not affected by abnormalities (Von Spiessen et al, 2015). Recep et al (2001) also say that IOP measurement is influenced by corneal thickness. Thick cornea causes falsely high IOP if the corneal thickness is due to increased collagen fibrils but in the case of corneal thickening caused by corneal edema low readings occur. Thin corneas produce falsely low readings of IOP. Johnson et al (2007) say that in rigid eyes surface IOP measurements are higher than in eyes that are more distensible.

Von Spiessen et al (2013) also say that it is also important to keep in mind the localization and angle of impact and distance of probe to the corneal surface. Also, it is paramount that the manufacturer's recommendations on handling have to be met because deviation from them significantly affect the results obtained. When compared to the reference measurement reducing the measuring distance to less than 4 mm from the cornea and altering the Tonovet onto the peripheral cornea (approximately 1,5 mm from the limbus) resulted slightly elevated IOP readings. With the angular deviation of the measuring axis, a substantial decrease of IOP occurred.

De Oliveira et al (2018) did a study where they assessed the variability of Tonovet rebound tonometer IOP measurements in the peripheral cornea and in angulated positions on the canine eye. IOP reading was taken at a number of different angles from the cornea: 1) perpendicularly at the center of the cornea, 2) at four different points on the peripheral cornea and 3) at the center of the cornea but the tonometer position was at four angles. All the measurements taken were compared to a measurement taken from the recommended position on central cornea. The outcome of the study showed that IOP values were significantly underestimated in seven positions but the dorsally angled measurement in the central cornea did not differ from those at the central cornea. The results from this study show that measuring in peripheral regions or angling of the tonometer can result in small but statistical underestimation of measured IOP values.

Safavi & Honarmand (2008) did a study where they researched the influence of head flexion after endotracheal intubation on IOP and cardio-respiratory response in patients undergoing cataract surgery. The authors say that endotracheal intubation and laryngoscopy most likely increase IOP significantly, at least 10...20 mmHg. The mechanism why these procedures cause the increase in IOP is not clear, but it is probably because of sympathetic cardiovascular response to tracheal intubation. After head flexion, there was an increase in IOP and this might be due to the tracheal mucosa stimulation by head flexion. This mechanism is also not clear but the authors suggest that it is likely because of aqueous outflow blockage by acute venous congestion or sympathetic cardiovascular response to flexion of the head. It is important to notice that any bucking, breath holding, straining or airway obstruction during anesthesia induction or maintenance will increase venous congestion in the ophthalmic veins and because of that a rise in IOP.

IOP measurements may be influenced also on the body position. Broadwater et al (2008) studied the effect of body position on IOP in dogs without glaucoma. They concluded that IOP decreased significantly on dogs when they were sitting or dorsally recumbent, but did not change significantly when the dogs were sternally recumbent. Body position should be consistent among repeat evaluations. Ghaffari and Gherekhloo (2017) did a study with cats where they investigated body position effect on IOP in clinically normal cats. They found that there is a significant increase in IOP when the cats are in dorsal position compared to the IOP observed in cats that were in sternal recumbency and lateral recumbency.

2. MATERIALS AND METHODS

2.1. The population of the study

The data was collected from 2018 fall to 2019 spring. 12 adult dogs of different breeds were included. There were 2 Yorkshire Terriers, 2 Tibetan Mastiffs, 1 German Shepherd Dog, 1 Siberian Husky, 1 Pomeranian, 1 German Wirehaired Pointer, 1 Caucasian Shepherd Dog, and 3 mixed breed dogs. There were 4 females, out of which all were spayed and 8 males, out of which 2 were neutered. The weight ranged from 3,8 kilos to 49 kilos. Each animal was obtained from the University of Life Sciences Small-Animal Clinic who were going to undergo orthopedic knee surgery. Informed owner consent was obtained (Appendix 1). Pre-anesthetic physical examination was done and blood work consisting of BUN and CREA in all cases. With reference values of 2,50...9,60 millimoles per liter (mmol/l) and 44,0...159,0 micromoles per liter (mikromoles/l) respectively. Blood pressure measurement was discarded because of the false high measurements that resulted from the anxiousness of the participants. All dogs were also divided into classes according to the American Society of Anesthesiologists (ASA) classification. All dogs were in class 1 (4 dogs) or 2 (8 dogs).

Before entering the study, all subjects went through an ophthalmological examination including outer inspection of the eye, Schirmer tear test, intraocular pressure measurement (first measurement, M_1) with rebound tonometry, pupillary light reflection, slit lamp biomicroscopy and direct ophthalmoscopy. All the examinations were done by the author of this thesis. The author was supervised to do the ophthalmologic examination by Estonian University of Life Sciences Small-animal Clinic ophthalmologist. The author of the theses was blinded at the time of ophthalmologic examination in which group the dog was going to end up in. Dogs who were deemed unhealthy on physical and/or ophthalmologic examination or with abnormal levels of BUN and CREA were excluded from this study. Brachycephalic breeds were discarded from the study because of their normally slightly higher IOP. Aggressive dogs that were difficult to handle were excluded from the study. Also, dogs that were strongly overweight according to The World Small Animal Veterinary Association Global Nutrition Committee Body Condition Score (BCS 7-9) were excluded. The dogs concluded had the BCS score of 5 (6 dogs) or 6 (6 dogs).

2.2. The intraocular pressure measurement technique

All measurements of IOP were taken by the author of this thesis using rebound tonometry (Tonovet tonometer, Icare Finland Oy, Helsinki, Finland) and both eyes were measured in all dogs at all time points. Only readings from the central cornea were obtained with the probe's point of contact being perpendicularly and approximately 4...8 mm from the corneal surface. Each IOP obtained from a subject was an average of 6 readings and only measurements with the acceptable standard deviation range (< 2,5% variance) as indicated on the Tonovet display were used. The baseline measurements were taken from dogs in the sitting position. Measurements subsequent after anesthetic premedication and induction were taken with the dogs held fixed in sternal position with the head raised to avoid pressure against the globe, jugular veins or eyelids.

2.3. Anaesthetic technique

Subjects were put in 1 of 2 treatment groups by random drawing, using a closed envelope containing the name of the drug combination that will be used. The 2 treatment groups were: Group MDP – methadone (0,3 mg/kg BW) [Synthadone vet 5 milligrams per milliliter (mg/ml) inj, Le Vet Beheer B.V., Wilgenweg, Oudewater, Holland] IV and dexmedetomidine (0,003 mcg/kg BW) (Sedadex inj. 0,42 mg/ml, Le Vet Beheer B.V., Wilgenweg, Oudewater, Holland) IV; Group MMP – methadone (0,3 mg/kg BW) (Synthadone vet 5 mg/ml inj, Le Vet Beheer B.V., Wilgenweg, Oudewater, Holland) IV and midazolam (0,25 mg/kg BW) (Midazolam Accord 5 mg/ml, Accord Healthcare Limited, Sage House, Middlesex, United Kingdom) IV. Both groups got also propofol (1 mg/kg BW during 15 seconds and then 0,5 mg/kg BW) (Propofol Fresenius 10 mg/ml, Fresenius Kabi Austria GmbH, Hafnerstrasse, Austria or Fresenius Kabi AB, Uppsala, Sweden) IV.

All subjects got an IV catheter gauge ranged from 20...24 gauge. An IV catheter was placed according to the Crow and Walshaw's Manual of Clinical Procedures in Dogs, Cats, Rabbits and Rodents, Fourth Edition (Boyle, 2016). Then methadone (0,3 mg/kg BW) was given to both groups IV. After the onset of methadone and when the clinical symptoms of methadone onset appeared (panting and miosis) approximately 5 minutes the second IOP measurement (M_2) in both groups were taken. Then group MDP got dexmedetomidine

(0,003 mcg/kg BW) IV. After the onset of dexmedetomidine approximately 5 minutes the third IOP measurement (M_3) was taken. With group MMP they got midazolam (0,25 mg/kg BW) IV and approximately 5 min after the onset of midazolam, the third IOP measurement (M_3) was taken.

5 minutes after the administration of either dexmedetomidine or midazolam both groups were given propofol (1–2 mg/kg BW during 15 min and then 0,5 mg/kg BW) IV until the loss of jaw tone. Then the fourth IOP measurement was taken (M_4) and the fifth IOP measurement (M_5) was taken right after intubation. After intubation, the animal was anesthetized with isoflurane (maintenance with 1,5% to 2,5%) (Isocare 1000 mg/g Inhalation Vapour, Liquid Isoflurane, Aesca Queenborough Ltd, Kent, United Kingdom). After intubation, the animal was put to dorsal or lateral recumbency depending on the operation the dogs were going to have. All the dogs were monitored during anesthesia by a veterinarian specialized in anesthesia. Animal's heart rate, respiratory rate, and pattern, mean arterial blood pressure, end-tidal carbon dioxide, pulse oximetry, and body temperature were monitored throughout the surgery.

2.4. Statistical analysis

The differences in IOP values between the two groups and time moments were studied with a general linear mixed model considering the fixed effects of the group (MMP and MDP), the moment of time (M_1, \dots, M_5) and group by time moment interaction. As there were two parallel measurements for each dog at each time moment (two eyes) and five times two repeated measurements (five moments of time and two eyes) of each dog in total, then these dependencies were considered by including in the model both the random effect of the dog and the random effect of the measurement pair corresponding to the same dog and time moment. The effect of the eye was omitted because it was not statistically significant ($p = 0.577$) and its inclusion did not affect the other results. The Tukey *post-hoc* test was applied to perform a pairwise comparison of the groups and the time moments. The relationships between dog's age, weight, BUN and creatine concentrations and IOP measured at different time moments were studied with linear correlation analysis. All results were considered statistically significant at $p \leq 0.05$. Statistical analyses were performed and all the figures were constructed with program R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria).

3. RESULTS

The measured IOP values and their change in time shown per individual dogs are presented in Figure 4. As at each time moment the IOP was measured in both eyes, for each dog, two lines are presented. In general, the two parallel measurements are quite similar. However, there are two dogs in group MMP with a higher discrepancy in their IOP measurements between two eyes. This indicates that to achieve higher accuracy and to notice potential errors it can be eligible to perform measurements in both eyes. On four dogs out of six dogs in group MMP, there is a visible increase in the IOP at the time moment M_4 after getting the drug propofol. Administration of methadone increased intraocular pressure in dogs (mean IOP at the time M_1 was 18.9 ± 1.34 mmHg and at the time M_2 21.8 ± 1.34 mmHg), however, this change did not turn out to be statistically significant ($p = 0.367$).

The general linear mixed model analysis revealed, that although the estimated IOP in group MDP was 2.1 mmHg lower than in group MMP (the average \pm standard error 19.6 ± 1.3 and 21.7 ± 1.3 mmHg in groups MDP and MMP, respectively), this difference was not statistically significant ($p = 0.281$). However, it follows from additional analysis, that at the time moment M_4 the IOP in group MMP was statistically significantly higher compared with group MDP ($p = 0.014$)(Figure 5).

The overall time effect was statistically significant ($p = 0.030$) and indicates, that the IOP values on the time moment M_4 were much higher compared with the previous and following time moments. And even though the group by time interaction effect was not statistically significant ($p = 0.126$), the effect of time appears mainly in the group MMP (Figure 5).

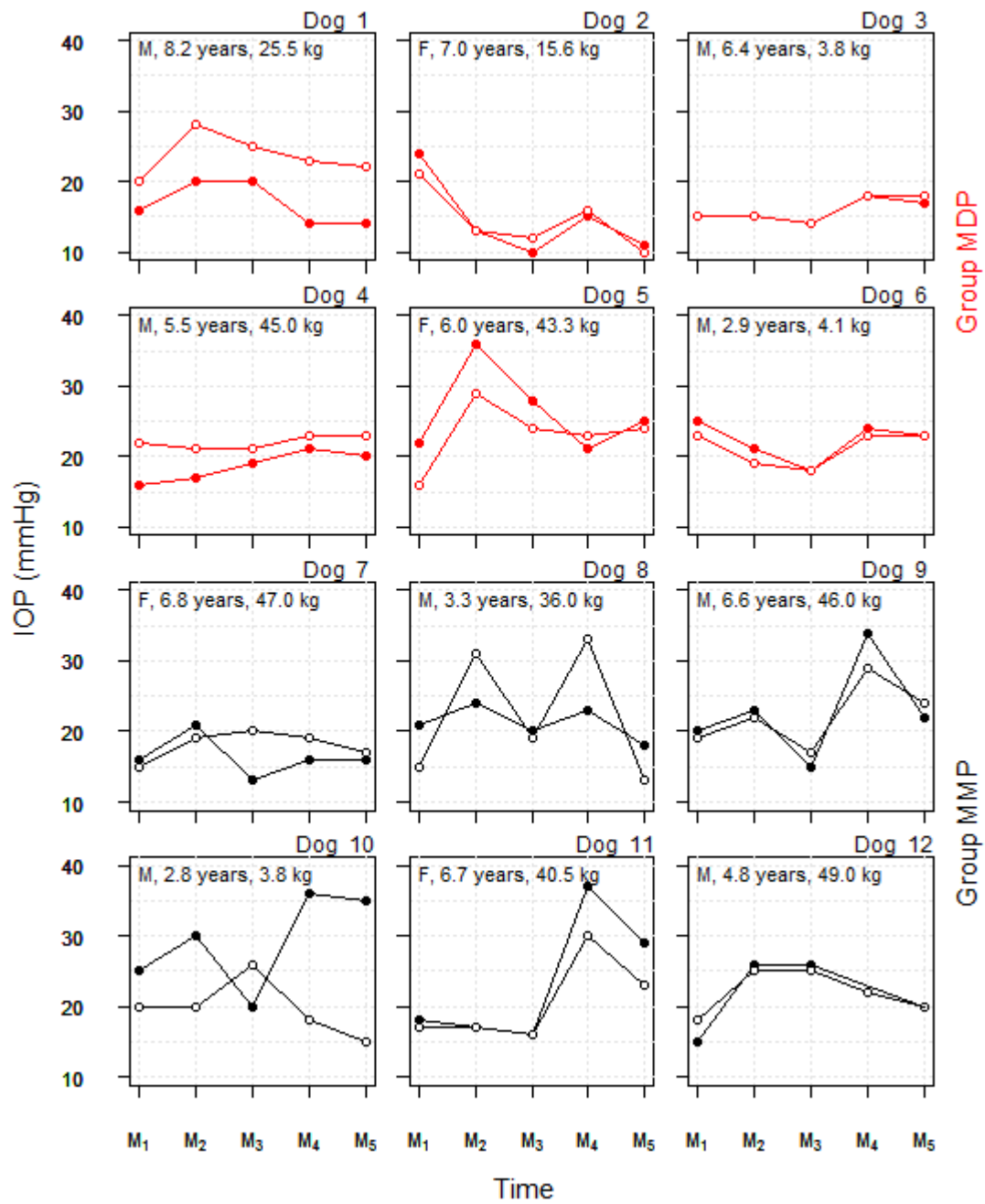


Figure 4. The IOP measurements of different dogs. The IOP measurements of different dogs – filled symbols denote the measurements in the left eye and empty symbols denote the measurements in the right eye, respectively. Group MDP dogs are denoted with red color and group MMP dogs with black color. For each dog sex (M or F), age in years and weight in kg are presented.

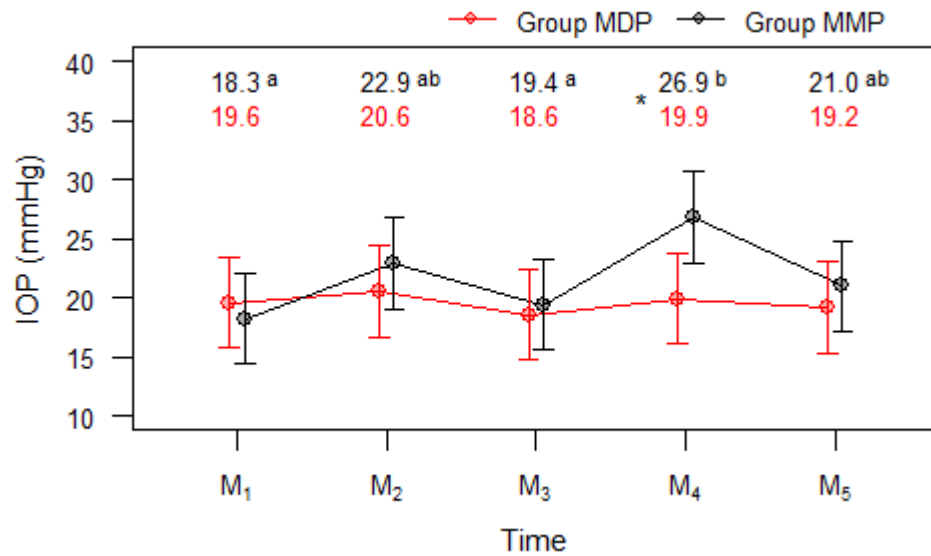


Figure 5. The IOP depending on group and time moment. The IOP depending on group and time moment: marginal means with 95% confidence intervals are presented; group MMP means without a common superscript letter are statistically significantly different ($p < 0.05$), Tukey *post-hoc* test), the star indicates the time moment with a statistically significant difference between group MMP and group MDP means.

Correlation analysis revealed, that there exist weak to moderate negative relationship between IOP and age and also weak to moderate positive relationship between IOP and BUN concentration. This means, that the IOP of older dogs is slightly lower and in case of higher urea concentration also IOP values are higher. These relationships were similar at each time moment indicating general consistent associations. However, none of these relationships were statistically significant (all $p > 0.05$). The IOP relationships with weight varied in time and the relationships with CREA concentration were close to zero (Figure 6).

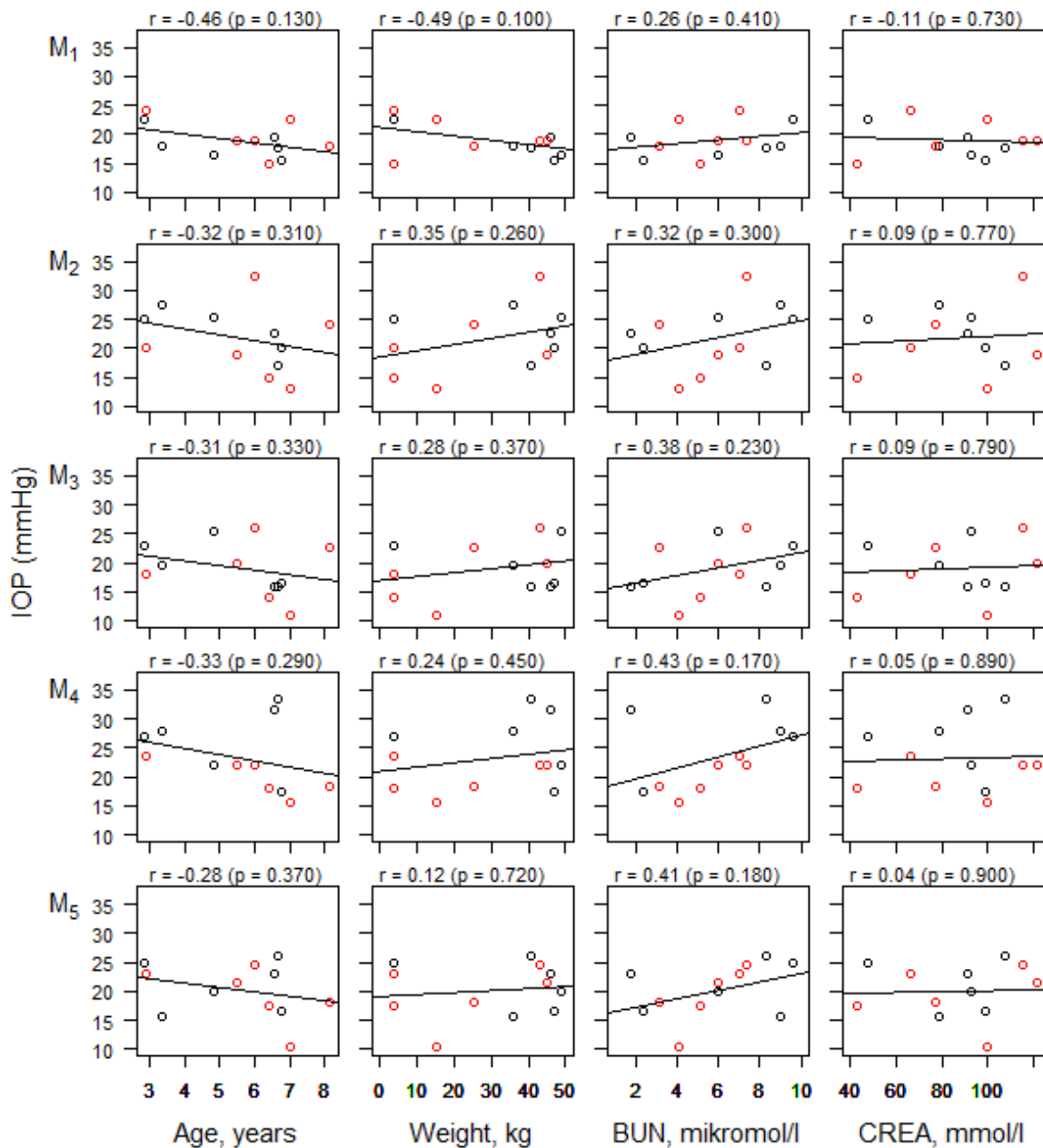


Figure 6. Relationships between dog's age, weight, BUN, and CREA concentration, and IOP measured at different time moments M₁–M₅. Relationships between dogs' age, weight, BUN, and CREA concentration, and IOP measured at different time moments M₁–M₅ (each row of scatterplots corresponds to IOP measurements at one specific time moment). In scatterplots red dots denote group MDP dogs and black dots group MMP dogs, lines indicate linear relationships and above each plot, the linear correlation coefficient with p-value are presented numerically.

4. DISCUSSION

There are many different theories and opinions that have been evaluated regarding which preanesthetic and anesthetic drugs should be used for ophthalmologic surgery on small animals (Tamura et al, 2002). In recent years there is much more information published regarding the effects of preanesthetic and anesthetic drugs on IOP in dogs, but still, there is very little information about the effect of methadone on IOP and also there is little recent information about how midazolam effects the IOP. This is also why the author of this thesis chose these two drugs used in anesthesia along with the other drugs.

In humans, opioids are indicated for ophthalmic procedures because this drug group reduces or prevents an increase in IOP (Tamura et al, 2002). In dogs, the literature says that opioids cause respiratory depression which increases the arterial partial pressure of carbon dioxide and that results in an increase of IOP because carbon dioxide causes vasodilatation and through that increases choroidal blood volume (Rauser et al, 2012). But at the same time, other factors like ocular hypotension and miosis of the pupil causes lowering of the IOP (Dortch-Carnes & Russell, 2006).

In this thesis, study methadone caused an increase of IOP. One reason why the IOP could have increased is the motion of panting which is a common side effect of methadone. With the motion of panting the facial muscles exert and through that the IOP may be increased. McMonnies (2016) also points out that muscle exertion may cause elevated IOP. This result should be considered with caution because of the small study population.

In the studies that the author of the thesis read IOP lowering was described after the IV administration of dexmedetomidine. The lowering of IOP happens through different mechanisms like the α_2 -adrenergic modulation of IOP and indirect hemodynamic effect (Artigas et al, 2012; Rauser et al, 2012; Smith et al, 2018). In this thesis work, dexmedetomidine decreased IOP like the other study authors describe and can be safely used in ophthalmological procedures.

Studies say that midazolam does not have a clinically important effect on the IOP (Artru, 1991; Ghaffari et al, 2010; Gunderson et al, 2013) and could even lower the IOP. The

decrease in IOP could be explained because midazolam is a muscle relaxant that also lowers the extraocular muscle tone (Tamura et al, 2002). In this thesis study, the author saw a lowering of IOP after 5 minutes of administration compared to the methadone measurement, but when comparing to the baseline IOP value there was no clinically significant effect and therefore is safe to use in ophthalmological procedures.

In recent years authors of different studies have seen a transient post-induction non-significant IOP rise, followed by a significant reduction after the administration of propofol. It remains unclear why this transient elevation of IOP happens, but some authors postulate that it happens because of drug effect on the central nervous system which alters the production and outflow of AH (Costa et al, 2015). Webb et al (2018) add that 2...4 minutes after propofol is given the rise on IOP is the highest.

In this study, the MMP group showed a significant increase in IOP after the administration of propofol and also this could be explained by the fact that the measurement was taken approximately 2 minutes after the administration of propofol. But with the MDP group, no clinically significant change was seen. The differences between groups could also be because of the interactions between dexmedetomidine and propofol or midazolam and propofol. The author of the thesis suggests that if in the future when the effect of propofol is evaluated on IOP repeated measurements should be done opposing to the only one after the jaw tone has gone absent. Probably propofol is safe to be used in ophthalmological procedures but only if the transient elevation of IOP is passed.

Also in this thesis, the effect of endotracheal intubation was evaluated. Safavi & Honarmand (2008) say that that endotracheal intubation and laryngoscopy most likely increase IOP significantly, at least 10...20 mmHg. They also saw an increase in IOP after head flexion and this might be due to the tracheal mucosa stimulation by head flexion. They saw a small increase in IOP after endotracheal intubation. In this thesis in the MMP group, a small rise in IOP was seen, but in the MDP group there was no rise in IOP. This result should also be considered with caution because of the small study population.

Safavi & Honarmand say that it is important to notice that any bucking, breath holding, straining or airway obstruction during anesthesia induction or maintenance will increase venous congestion in the ophthalmic veins and because of that a rise in IOP. The author of this study also suggests that this should be considered when evaluating the IOP.

When comparing the groups MDP and MMP the author concludes that a better anesthetic regimen for ophthalmological procedures is MDP because the IOP remains relatively consistent and there are no acute rises in IOP during preoperative period.

Also, correlation analysis was done to research the correlations between IOP at different time moments M_1 – M_5 and the dog's age, weight, BUN, and CREA concentration. However, none of these relationships were statistically significant (all $p > 0.05$). Although the negative correlation was seen between age and IOP. Which means that the older the dog, the lower the IOP. Pizzirani & Kong (2015) also say that baseline IOP in dogs decrease with the increase of age.

Another correlation was seen between BUN concentration and IOP. The higher the BUN concentration in blood the higher was IOP. Wong et al (2014) also say that the urea gradient generated between blood and the AH causes water to move to the anterior chamber of the eye and thus increasing the IOP. Chelala et al (2015) say that higher AH osmolarity compared to lower plasma osmolarity and a relative increase in the AH urea concentration may contribute to IOP elevation. All the results gotten from this study should be interpreted with caution because of the fact that the study population was very small.

5. CONCLUSIONS

The aim of the present study is to evaluate and compare the effect of two preoperative anesthetic regimens MDP and MMP on IOP in dogs before general anesthesia with isoflurane. As a result, the statistical analysis showed that the MDP and MMP groups were quite similar.

There was an increase in IOP after methadone administration and therefore should be used with caution in ophthalmological procedures or with patients that have an ocular disease. Dexmedetomidine lowered the IOP and with midazolam, there was no clinically significant effect and therefore can be safely used in ophthalmological procedures. With propofol administration in the group MDP, no clinically significant change in IOP was seen, but in the group, MMP showed a statistically significant increase on IOP after propofol administration. When using propofol the transient elevation of IOP needs to be passed.

The author of the thesis suggests that if in the future the effect of propofol is evaluated on IOP, repeated measurements should be done opposing to the only one after the jaw tone has gone absent. Endotracheal intubation did not cause a change in the IOP in the MDP group but a small rise in IOP was seen in the MMP group.

When comparing the groups MDP and MMP groups the author thinks that the better anesthetic regimen for ophthalmological procedures is the MDP group because the IOP remains relatively consistent throughout the preoperative period and there are no acute rises in IOP.

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ÜLDKOKKUVÕTE

Kahe erineva preoperatiivse anesteetilise režiimi mõju silma siserõhule koertel

Lõputöö eesmärk oli hinnata ja võrrelda kahe erineva preoperatiivse anesteetilise režiimi MDP ja MMP mõju IOP-le koertel. Selleks uuriti 12 erinevat tõugu täiskasvanud koera, kes tulid Maaülikooli väikeloomakliinikusse selektiivsele ortopeedilisele põlveoperatsioonile. Iga loomaga tehti anestesieaeline kliiniline ülevaatus ja vereanalüüs, mis koosnes vere uurea lämmastikust ja vere kreatiniinist. Kõik loomad läbisid oftalmoloogilise ülevaatus. Statistilised analüüsid ja joonised koostati programmiga R versiooniga 3.5.3 (R Foundation for Statistics Computing, Viin, Austria).

Statistilise analüüsi tulemus näitas, et gruppidel MDP ja MMP olid üsna sarnased toimed. Samuti uuriti endotrahheaalse intubatsiooni mõju IOP-le ning statistiline analüüs näitas, et endotrahheaalne intubatsioon ei põhjustanud IOP muutust grupis MDP, kuid grupis MMP oli näha kerge IOP tõus pärast endotrahheaalset intubatsiooni.

Pärast metadooni manustamist suurenes IOP ja seetõttu tuleb silmasiseste operatsioonide ja silmahaigustega patsientide puhul kasutada metadooni ettevaatlikusega. Deksmetomidiniin alandas IOP-i ja midasolaamil ei täheldatud kliiniliselt olulist toimet, mistõttu võib neid ravimeid ohutult kasutada oftalmoloogilistes protseduurides. MDP grupis ei täheldatud kliiniliselt olulisi muutusi, kuid MMP grupis täheldati IOP-i märkimisväärset suurenemist. Propofooli kasutamisel peab mööduma propofoolist tingitud IOP-i mööduv tõus. Lõputöö autor soovib, et kui tulevikus tehakse uuringuid, mis hindavad propofooli mõju IOP-le, tuleb teha korduvaid mõõtmisi pikema aja jooksul, et hinnata propofooli mõju IOP-le täpsemalt.

MDP ja MMP gruppide võrdlemisel on lõputöö autori seisukoht, et parem preoperatiivne anesteetiline režiim oftalmoloogilisteks protseduurideks on MDP, sest IOP jääb perioperatiivse perioodi ajal suhteliselt stabiilseks ja IOP-s ei ole ägedat tõus

APPENDICES

Appendix 1. Informed owner consent

Lugupeetud loomaomanik,

Teie poole pöördub Eesti Maaülikooli veterinaarmeditsiini õppekava tudeng Triinu Lomp palvega, et võiksime kaasata Teie looma oma teostatud uuringus. Uuringu teemaks on kahe erineva anesteetilise režiimi mõju silma siserõhule tervetel koertel.

Uuringusse haaratakse võimalikult palju loomi, kes tulevad selektiivsele põlveoperatsioonile Eesti Maaülikooli Väikeloomakliinikusse ortopeedi juurde. Uuringus osalemine on vabatahtlik ning uurimusse kaasatakse ainult need loomad, kelle omanikud annavad kirjalikult loa looma uuringusse kaasamiseks. Teie ja Teie looma andmeid jäävad anonüümseks. Selle kindlustamiseks saab Teie loom viie kohalise numbrikombinatsiooni ning mõõtmistulemuste andmete statistiline analüüsis toimub läbi saadud numbrikombinatsiooni. Uuringu etappideks on:

- looma kliiniline ülevaatus, enne operatsiooni neeru biokeemiliste näitajate määramine vereseerumist
- looma silma ülevaatus ärkvel olekus ning silma siserõhu mõõtmine mitteinvasiivsel meetodil
- silma siserõhu mõõtmine anesteesia erinevates etappides

Käesoleva uuringu eesmärgiks on võrrelda kahe erineva anesteetilise režiimi mõju silma siserõhule ning saada seeläbi informatsioon, kas neid ravimeid saab kasutada ohutult mitte ainult ortopeedilistel vaid ka silma operatsioonidel. Taolist uuringut ei ole Eestis läbi viidud.

Anesteetilised ravimid, mida kasutame Teie looma peal on rutiinsed ravimid, mida kasutatakse ortopeedilistel operatsioonidel anesteesia läbiviimiseks ning mis on ülemaailmselt heaks kiidetud Maailma Väikelooma Veterinaarmeditsiini Ühingu (inglise keeles *World Small Animal Veterinary Association*) poolt. Silma siserõhu mõõtmine ei ole loomale valus ega ebameeldiv. Neeru funktsiooni biokeemilised näitajad (kreatiniin ja urea) võetakse läbi veenikanüüli, mis paigaldatakse rutiinselt enne igat anesteesiat ja operatsiooni. Tegelikult on neeru biokeemiliste näitajate määramine enne igat anesteetilist

Appendix 1 continuation

protseduuri soovituslik, et välistada neerude kahjustamist. Seega Teie loomale ei valmistata üleliigset ebamugavustunnet ja valu. Kui näeme, et Teie loom on stressis ning käsitlemine on talle ebameeldiv, siis katkestame uurimise eetilistel kaalutlustel ning tugeva stressi mõjul tõttu mõõdetavatele parameetritele. Teie kui loomaomanik ei pea uuringus tehtud protseduuride ega kasutatud materjalide eest maksma.

Anname hea meelega ka tagasisidet uurimise käigus leidudest (silmaülevaatus tulemused ja silma siserõhu tulemused ning neerunäitajate tulemused). Teil on õigus uuringus osaleda või keelduda uuringus osalemisest, Te võite ka oma loa tagasi võtta sellest töö autorit teavitades. Loa tagasi võtmise põhjust ei pea Te avaldama.

1. Kas olete nõus, et Teie loom osaleb veterinaarmeditsiini 6. kursuse tudengi Triinu Lomp poolt läbi viidud uuringus, kus võrreldakse kahe erineva anesteetilise režiimi mõju silma siserõhule? **Jah** **Ei**

2. Kuidas soovite tagasisidet Teie loomalt saadud tervise parameetrite osas (Palun tämmake Teile sobivale viisile joon alla)?

- Loomale järele tulles silmast silma
- Telefoni teel (Palun kirjutage telefoni number)
- Meili teel (Palun kirjutage meili aadress)
- Ei soovi tulemusi teada

.....

.....

Teie nimi ja allkiri

Kuupäev

Appendix 2. Non-exclusive license for depositing the final thesis

Non-exclusive license for depositing the final thesis and opening it for the public and the supervisor's (supervisors') confirmation for allowing the thesis for the defense

Hereby I, Triinu Lomp
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