The applications of sub-Tenon's anaesthesia for canine ophthalmic surgery

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Abstract

Sub-Tenon's anaesthesia is an indispensable anaesthetic technique in human ophthalmic surgery. It produces highly effective regional anaesthesia and has a significantly lower complication rate than the previously used peribulbar and retrobulbar injections. Although this technique has potential application to veterinary ophthalmology it has not yet been reported in clinical cases. This thesis reviews the literature that references local anaesthesia for ocular surgery in human and veterinary ophthalmology. A sub-Tenon's block technique that was specifically developed for use in dogs is also described. This technique is assessed with a prospective controlled clinical study testing this technique across a variety of ocular surgeries including enucleation, intrascleral prosthesis, keratectomy with a third eyelid flap and cataract surgery. The effect of sub-Tenon's anaesthesia on specific parameters was recorded and compared to the controls such as; globe position and rotation, pupillary dilation, general anaesthetic monitoring parameters, intraocular pressure, vitreal expansion and post-operative pain scores. Analysis of these parameters has indicated that sub-Tenon's anaesthesia was an effective option for controlling post-operative pain when used in conjunction with systemic analgesics and was an excellent alternative to systemic neuromuscular blockade for canine cataract surgery.

Abbreviations

STB - Sub-Tenon's block

NMB - Neuromuscular blockade

IOP - Intraocular pressure

SK - Superficial keratectomy surgery

ISP - Intrascleral prosthesis surgery

$ETCO_2$ - End tidal carbon dioxide

Iso% - Isoflurane vapouriser setting

HR – Heart rate

RR – Respiratory rate

BPsys – Systolic blood pressure

BPmean – Mean blood pressure

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CHAPTER 1

A review of local and regional anaesthesia in human and veterinary ophthalmic surgery

Introduction

Regional anaesthesia is the cornerstone of anaesthesia and analgesia for a variety of ocular surgeries performed in humans. It allows intricate surgery to be performed, often without general anaesthesia. In veterinary ocular surgery, general anaesthesia is almost always required for patient immobilisation. As a result, local and regional anaesthesia in veterinary patients has not developed as far as in human ophthalmology and the amount of veterinary scientific literature on the topic is significantly less than for humans. Nonetheless, local anaesthesia has many potential benefits for veterinary ophthalmic surgery by providing superior analgesia, anaesthesia and operating conditions for a variety of procedures. This chapter reviews the current knowledge of local and regional anaesthesia for ocular surgery from the human scientific literature as is pertinent to veterinary species. Veterinary specific references are utilised when possible to provide a comprehensive review.

Historical origin of local anaesthesia agents and techniques

Prior to the usage of specific anaesthetic agents a variety of other techniques were used to aid the performance of surgical procedures. These included: hypnotism, faith, hypothermia, tourniquets and a variety of narcotic extracts, with the success of eye operations greatly dependent on the speed of the surgeon and the stoicism of the patient.(2) The introduction of ether in 1846, followed by chloroform allowed induction of general sedation or anaesthesia, although the results were less than satisfactory.(2) The development of a hollow needle that allowed hypodermic injections, by Alexander Wood in 1853, provided the ability to introduce drugs into tissues and into direct contact with the associated nerves.(2)

The first major development in local anaesthesia was the identification of the anaesthetic properties of cocaine, an alkaloid extracted from the coca plant (family Erythroxylaceae). The general effect of chewing coca leaves had been known for centuries, however the specific active agent wasn't discovered until 1855.(10) Subsequently it was shown to block the corneal reflex in animals after topical application of a solution.(11)

The modern era of ophthalmic surgery began in 1884 with the introduction of cocaine by Koller as a local anaesthetic. This allowed surgery to be performed on the eye in conscious patients without causing pain.(12) Reports of enucleations performed with the use of cocaine soon followed, however the simple and effective method of a retrobulbar injection described

by Knapp was quite revolutionary.(13, 14) As a 1-4% solution cocaine had an onset of action after approximately 30 seconds, and about 10 minutes duration of action.(15) However, enucleation under local anaesthesia with cocaine was not met with general approval due to the significant toxic effects on the central nervous system and cardiovascular system and the sympathomimetic effects that followed the use of the concentrated 4% cocaine solutions.(2, 15) The toxicity of cocaine was quickly realised, but not before many serious adverse effects had occurred, particularly in general surgery that used larger doses than ophthalmic surgery.(2)

Once the chemical composition of cocaine was discovered by Einhorn in 1899, the synthetic preparation of new compounds could begin including holocain, eucain, stovain, butyn, alypin, and procaine.(2, 16) Lidocaine was developed by Lofgren in 1943, quickly becoming the most widely used local anaesthetic from 1948 onwards, and acting as a prototype for the synthesis of other amide linked local anaesthetics.(15, 17)

Outline of pain, neural pathways and sensitisation

An understanding of the basic pain pathways is required to plan an effective analgesic protocol for patients and for creating experimental studies assessing pain. The pain experience can be divided into four components - transduction by the nociceptors, transmission of the stimuli up sensory neurons, modulation in the spinal cord and sub-cortex, and conscious perception in the somatosensory cortex. The effect is the sensory and emotional experience that we describe as pain. A summarised outline of a noxious stimuli's journey up the pain pathway is as follows.(18-23) Peripheral polymodal nociceptors are stimulated and the impulse is transmitted up axons of c and Aσ sensory fibres to neural cell bodies located in the dorsal horn of the spinal cord and brain stem. Here the impulse undergoes a level of processing with influence from modulatory interneurons, descending inhibitory neurons and endogenous analgesic mechanisms. Second order ascending neurons project the impulse towards the brain and motor neurons in the ventral horn are activated to create an 'avoidance' reflex arc. The ascending neurons synapse in the thalamic region before the impulse moves through other areas of the brain (including the limbic system) on its way to the somatosensory cortex. The spinal cord transmission of noxious stimuli to the brain can be explained by the 'gate control theory', initially proposed by Melzack and Wall in 1965.(24) This describes the theory that afferent nerve fibre impulses are modulated by the spinal gating mechanism in the dorsal horn

of the spinal cord prior to the conscious perception of pain by somatosensory cortex. The impulse is modulated by the relative amount of large and small diameter nerve fibre activity, excitatory and inhibitory signals that descend from the brain; and a specialised system of rapidly conducting fibres that activates selective modulatory cognitive processes. When the output of the spinal cord transmission exceeds a critical level, the action system is activated. The action system consists of neural areas that underlie the complex, sequential patterns of behaviour and experience that are characteristic of pain.(24) This results in the experience of pain being influenced by a great number of factors, which shows that it is not a simple straight-through sensory system as was initially proposed by Descrates' three centuries ago.(23) The key pathways that result in the great variation of pain experienced by individuals are within the modulation step. The innate ability of the nervous system to reduce pain signals that are received by the higher centres are affected by factors within the individual and the environment, most of which are poorly understood. This results in pain being a unique experience to each individual and therefore difficult to accurately predict.(25) The endogenous analgesic pathways can be unregulated in response to pain, therefore reducing the intensity of the stimuli through time and having a positive effect on the individual. However the opposite effect can occur with chronic pain which results in sensitisation and an increasingly elevated level of pain.

Nociceptive pathways can be sensitised peripherally or centrally. Peripheral sensitisation is manifested by hyperalgesia in the region of interest.(21, 26) After tissue injury or surgery, inflammatory cells congregate in the area and release cytokines that amplify and potentiate the inflammatory response.(21, 22, 27) This localised reaction causes a patient to react to low intensity stimuli as for a painful stimuli due to an increased sensitivity of nociceptors.(18, 21) Central sensitisation ('windup') occurs when untreated peripheral sensory neuron activity drives central spinal systems that amplify and prolong the incoming sensory messages. This occurs as the neurons increase their sensitivity to the local reaction, enhancing the frequency and intensity of pain stimuli to the brain and results in a dissociation of the final pain sensation from the peripheral activity.(21, 22, 26-28) The creation of long lasting action potentials from the influence of glutamate, neuropeptides and positive feedback loops, result in a progressive increase in the depolarisation of dorsal horn neurons. This causes a perpetuating state where a single noxious stimuli can lead to several minutes of post-synaptic depolarisation.(20, 27) This cumulative depolarisation primarily results from activation by glutamate of N-Methyl-D-Aspartic acid (NMDA) receptors.(21, 27, 28) Collectively these neurological changes result in development of allodynia, a decrease in the level of stimulation required to cause pain;

hyperalgesia, an exaggerated responsiveness to a suprathreshold stimuli; and secondary hyperalgesia, spread of hypersensitivity to non injured tissue.(18, 22, 27, 28)

A major issue with studying pain in animals is that true perception of pain in the higher brain centres cannot easily be measured, only inferred by assessing other variables like behavioural changes.(19, 20) Unfortunately these measures are fraught with inconsistencies between patients and are affected by other, non-pain related factors.(19) There are also considerable differences in assessing pain between individuals, breeds and species.(20, 29) Nonetheless post-operative pain scoring is an important analgesia assessment technique utilized in both the human and veterinary fields. There are a variety of different approaches, with a numerical cumulative pain scoring system currently preferred in veterinary ophthalmic studies.(30-35) This system was adapted from a similar approach used to assess post-operative pain following surgical procedures including ear canal ablation, laparotomy, shoulder arthrotomy, thorocotomy and stifle surgery.(36-40) The studies with a negative analgesic control group consistently show elevated pain scores with this system in the control cases.(30, 33, 40) This provides a level of validation for these pain scoring techniques, therefore making them a viable option for veterinary post-operative pain scoring studies.

Pain not only impacts significantly on the basic welfare of an animal, but in a surgical situation pain is highly likely to contribute negatively to the overall recovery of the patient. Pain is a stressor, therefore these responses are very similar to those that occur from any stress and affect the cardiorespiratory, metabolic, immune and wound healing processes.(18, 19) In one human study, it was found that the only predictor for speed of recovery and return to normal function after surgery was the total amount of pain experienced during a seven day post-operative period.(41) Other human studies have shown that high anxiety patients experience more post-operative pain, although this is not consistent and may be influenced by the population studied.(41-44) Veterinary patients have also been noted to regain normal functions sooner if pain is controlled immediately post-operatively.(19, 45) It is surprising that there is a relative paucity of published studies that have evaluated this, however pain scoring in its current form may not be very effective at detecting post-operative pain.(46) This is probably due to the complexities and variables in nociceptive pathways, marked individual variation in response to pain and the assessment situation, and the considerable difficulty assessing the actual impact of pain on veterinary patients.

Overview of analgesic techniques

Providing optimal analgesia needs to be a priority when performing surgical procedures on any patient. This is particularly important for veterinary species due to the inability of animals to effectively communicate their levels of pain, and our relatively insensitive pain measuring ability. Pain should be continually anticipated and pre-empted with therapy for as long as the abnormal afferent barrage of nerve stimulation from the wound and surrounding site continues.(27) This is achieved by using analgesic techniques targeted at three sites: peripheral nociceptors; sensory inflow via neurons; and the central nervous system.(27) Pre-emptive multimodal analgesia achieves the best results for analgesia in surgical patients.(21, 26, 47-51) Many studies have shown that patients that receive analgesic drugs before a painful stimuli experience less pain than patients that receive analgesia after the painful stimuli. This is because administering pre-emptive analgesia prevents central sensitisation occurring during surgery. Usage of multiple different analgesic drugs (multimodal) has the benefit of affecting different regions of the pain pathway; and therefore the analgesic effects will summate. For the purposes of this review, only the effects of local anaesthetics will be covered in depth, however a basic discussion of the other available analgesic drugs follows.

The initiation of the pain pathway begins with transduction of a noxious insult that stimulates the peripheral nociceptor, either by mechanical trauma or marked physiological insult. When peripheral sensitisation has occurred with the inflammatory response after the insult, anti-inflammatory medication can have analgesic effects. Non Steroidal Anti-inflammatory Drugs (NSAID) or corticosteroids are commonly used. There are also some analgesic effects at the nociceptors from local anaesthetics.(18, 19, 21, 22)

Transmission of the noxious stimuli up the nerve fibres towards the central nervous system can also be manipulated with analgesics. Pre-emptive local anaesthesia will completely prevent transmission of the stimuli and treatment with alpha-2 agonists will modulate the impulse.(18, 19, 21)

Modulation of the noxious stimuli at the level of the spinal cord provides the opportunity to manipulate the central nervous system's response through several different pathways.

Analgesic drugs that are active in the central nervous system include: opioids, alpha-2 agonists, dissociative agents, gabapentin, NMDA antagonists, local anaesthetics, NSAID, tricyclic antidepressants, cholinesterase inhibitors and anticonvulsants.(18, 19, 21, 52, 53) Sedatives are important for any surgical planning to reduce stress and anxiety, but as some have no analgesic properties (e.g. Acepromazine) they should only form a part of a greater analgesic approach.(18)

General anaesthesia blocks the pain pathway by preventing conscious perception of the noxious stimuli and provides immobilisation so reflex arcs are ineffective. General anaesthesia at light planes probably does not prevent peripheral and central sensitisation, as it has no effect on the nociceptors or their neurons, therefore transmission nociception still occurs to the level of the spinal cord.(18, 20, 54) This highlights the importance of using adjunct analgesic drugs to control pain in the post-operative period. Altering conscious perception is a pre-requisite to achieve surgical planes of general anaesthesia, and can be achieved through a variety of injectable and inhalational anaesthetic agents.(55) Due to the significant detrimental systemic effects of these drugs, and the risks associated with general anaesthesia, prolonged use for the purposes of analgesia are not a viable option.

Analgesia with local anaesthesia

Several local anaesthetic techniques have been described that allow a variety of ocular surgical procedures to be performed without general anaesthesia.(56-61) For human surgeons, this allows a greater turnover of patients at a lower cost. For veterinary patients, it can provide surgical treatment options while avoiding general anaesthesia, which is of particular benefit in high anaesthetic risk patients. These regional local anaesthetic techniques are most commonly used for equine and bovine ophthalmic surgery to avoid the risk of a poor recovery from general anaesthetic in horses and to provide a safe and practical option for production animal ophthalmic surgery.(62-64)

The importance of adjunct local anaesthesia with a general anaesthetic was first theorised by Crile, who stated `Patients given inhalational anaesthesia still need protection from stressful surgical stimuli by regional anaesthesia, otherwise they might suffer persistent central nervous system change`.(65) It was suggested that the use of regional anaesthesia blocks with general anaesthesia should be used to prevent post-operative pain in humans and prevent the

formation of painful scars caused by changes in the central nervous system due to noxious stimulation at surgery.(65) There have been many trials reported across a variety of surgical procedures that have found that local anaesthesia combined with general anaesthesia results in less post-operative pain than systemic analgesia combined with general anaesthesia.(26, 30, 37, 47, 54, 66-78) In addition, the local anaesthetic benefit may last for prolonged periods after surgery and in one study the benefit lasted up to 10 days.(54) This length of effect far exceeds the length of drug activity. It is thought that this prolonged analgesic effect is due to prevention of central sensitisation establishment by blocking peripheral sensory input at the time of surgery or before the patient has recovered from anaesthesia.(54) Some studies indicate that local anaesthesia appears to be a more effective analgesic when given pre-operatively compared to post-operatively. Theoretically, this abolishes peripheral sensation before the surgical trauma, preventing development of central sensitisation.(26, 27, 68, 79) However, there are studies where the pre-operative benefit is not clear cut.(26, 75) This may relate to the fact that tissue damage will result in two phases of sensory input, firstly from the surgical trauma and secondarily from the tissue inflammatory reaction during wound healing.(27) Therefore a single pre-emptive treatment may not be sufficient to eliminate post-operative pain sensitivity.

There has been some veterinary research on the benefits of regional anaesthesia as an adjunct to improve post-operative analgesia. The results of those studies have been mixed with some showing a benefit(30, 37, 78) while others did not detect a difference when compared to a systemic opioid.(36, 80) One study in children undergoing strabismus surgery, found that children who received pre-operative local anaesthesia were less likely to handle the eye dressing post-surgery.(73) This could be cautiously extrapolated to animals and their risk for self-trauma after surgery.

Pharmacology of local anaesthetics

Local anaesthetic agents share a common structure consisting of a hydrophobic/lipophilic aromatic ring (benzoic acid derivative), an amide or ester intermediate linkage site, and a hydrophilic secondary or tertiary amine.(17, 81, 82) Variations of the components within this structure can affect the drugs' characteristics. The hydrophobic portion enables diffusion through nerve cell membranes. Increasing hydrophobicity increases the potency and also toxicity of the agent.(17, 81) The hydrophilic portion may exist as an uncharged poorly water

soluble tertiary form, or as a positively charged quaternary form with an ammonium ion.(17, 81) This amphoteric structure acts as an on/off switch, allowing it to be both water and lipid soluble, and plays a pivotal role in the sequence of events leading to a conduction block.(17) For the local anaesthetic compound to be suitable for injection, it is formulated as water soluble quaternary hydrochloride salt.(17) The time of onset of action is predicted by the proportion of molecules that are in the tertiary, lipid soluble structure when it is exposed to physiological pH of 7.4.(17) The ionisation constant, pka, predicts the proportion of molecules that exist in each of these states.(17) The pka is defined as the pH at which 50% of the molecules are tertiary and 50% are quaternary.(17) All local anaesthetics have a pka greater than 7.4, therefore more molecules are in a quaternary state after injection. In addition, an inflamed acidic environment favours further quaternary conversion and explains why it can be difficult anaesthetising inflamed tissue.(15, 17) Local anaesthetics with a pka closer to 7.4 will have a more rapid onset of action, as there will be proportionally more of the lipid soluble compound that can penetrate into the nerves and it will be less irritating to tissue due to a reduced pH change upon injection.(17) The intermediate chain linkage provides a classification basis and determines the pattern of biotransformation for excretion, as esters are hydrolysed by plasma esterase's, and amides are biotransferred in the liver.(17) Currently, topical preparations tend to be esters and injectable solutions are more commonly amides.

All local anaesthetics share a similar mode of action by reversibly binding to sodium channels in neuron axons. This prevents sodium access to the axon and prevents conduction of an action potential in both motor and sensory neurons.(15, 17, 20, 83, 84) Local anaesthetics vary in their tendency to bind to plasma proteins. This correlates with the rate of binding to proteins within neuron sodium channels and is correlated to the duration of action of the drug.(17)

Neurons vary in their sensitivity to local anaesthetics. The requisite number of sodium channels can be blocked more rapidly in narrow bore neurons that are rapidly firing, therefore the order of neuron susceptibility from highest to lowest is autonomic, sensory, somatic motor, and the block resolves in the reverse order of nerve types.(85, 86) As the sensory Aσ and c fibres are more susceptible to its effects than the motor fibres that are large and heavily myelinated fibres, sensory function and pain perception is lost before motor function.(2, 20,

87, 88) This allows assessment of the block given, even in an anaesthetised patient, by recognising that if motor function has been lost, then sensory function will also be lost.

The duration of action increases with drug concentration up to a maximum, but high concentration formulations may be more irritant to the surrounding tissue and are a higher risk for developing toxicity.(15, 89) A common practice is to mix different types of local anaesthetics to attain properties from both drugs. For example, a mix of lidocaine and bupivicaine is reported to have the quick onset of action of lidocaine, with the length of activity of bupivicaine.(15, 89, 90) These benefits seem fairly anecdotal and as the toxic effects of the mixed local anaesthetics are additive, the safety index is not improved by mixing.(15)

Systemic signs of local anaesthetic toxicity include central nervous system, cardiovascular and gastrointestinal signs with: depression, seizures, muscle fasciculations, vomiting, bradycardia and hypotension.(83, 84) Local anaesthetics are rapidly metabolised by the liver, and treatment for the adverse effects is generally symptomatic until the drug is metabolised and excreted, but seizures can be controlled with intravenous diazepam if needed.(15, 81, 83) Seizures are the primary life threatening consequence of toxicity and presumably occur due to the selective depression of inhibitory tracts in the central nervous system, which allows the excitatory tracts to be unchecked in their activity.(17) The cardiovascular depressant effects appear to have a fairly long gradient of progression that is dose dependent, therefore there is a margin between cardiovascular depression and cardiovascular arrest.(91)

Topical local anaesthetics are epitheliotoxic with prolonged use and can cause a range of corneal pathology including: delayed wound healing from inhibition of mitosis and epithelial regeneration, alterations in local metabolism, immune mediated effects, superficial punctate keratitis, corneal oedema and diffuse necrotizing keratitis.(15, 81, 82) Corneal damage after treatment with topical anaesthetics can be due to direct affects of the drug or indirectly from damage after rubbing the eye while it is anaesthetised and should not be used therapeutically as local analgesia for surface ocular disease.(15)

Specific local anaesthetic agents

The properties and pros and cons of commonly used local anaesthetic agents are described below. Many of the published dose rates have very little to no peer reviewed supporting evidence of their efficacy or safety in veterinary patients. The published dose rates are largely extrapolated from human work or are anecdotal, and clinical judgment should be used when using these drugs.

Lidocaine (Lignocaine)

Lidocaine is an amide class local anaesthetic that has many different therapeutic properties,(81) of which only the anaesthetic and analgesia properties relevant to regional anaesthesia will be discussed here. It has a relatively quick time to onset of action of 2 to 10 minutes, a duration of surgical anaesthesia of 35 to 136 minutes and a post-operative analgesic effect which can last for several hours.(15, 20, 88, 92) Lidocaine has a pka of 7.8 and is rapidly metabolised by the liver, giving a reported plasma half-life in healthy dogs of 0.9 hours.(81) Dosing recommendations in dogs vary from 2-8mg/kg intravenously, or up to 4mg/kg regionally infused for both cats and dogs.(81, 83) As a rule, the dose for any local anaesthetic used regionally should not exceed the maximum safe systemic dose. Some studies assessing toxic doses of lidocaine in dogs showed a neurotoxic dose of 11-22mg/kg intravenously,(53, 92-94) and a highly variable intravenous fatal dose of 16-127mg/kg.(91, 92, 95) The fatal intravenous dose in cats was found to be generally lower at 47mg/kg.(81, 96) It has been recommended to be more cautious with dosing in cats that are systemically unwell or under general anaesthesia, (81) though this may be more of a theoretical concern as there are no published reports of higher complications rates in ill or anaesthetised cats. The toxic effects occur more commonly with higher concentration formulations (e.g. 4%) so use of 1-2% formulations is recommended, and these lower concentration solutions seem to have an equivalent anaesthetic effect.(15, 89) Lidocaine is primarily used as an injection for nerve blocks or regional anaesthesia, however it has also been investigated as a topical anaesthetic for cataract surgery, as part of a topical dermal anaesthetic cream (EMLA), and as a systemic constant rate infusion.(19, 21, 52, 53, 59, 81, 97)

Bupivicaine

This drug's reported onset of action varies from 2.5 to 30 minutes, with a long duration of action of between 2 to 12 hours.(15, 20, 81, 85, 88) With retrobulbar injections, akinesia can last for 6 to 10 hours, and partial extraocular paresis for 1 to 2 days.(15) Bupivicaine is about

four times more potent than lidocaine due to its increased lipid solubility, and therefore it is four times more toxic at a equivalent dose, which is why it is commonly used as a 0.25% or 0.5% solution.(15, 17) It also has the greatest percentage of protein binding of the available local anaesthetics and is the longest acting.(17) The pka is quite high at 8.1 and it has a reported plasma half-life in humans of 210 minutes.(17, 85) Systemic doses for dogs and cats are recommended to be no more than 1-2mg/kg.(83) Approximate neurotoxic intravenous doses for dogs are 4.3-5mg/kg,(93, 94) with fatal intravenous doses of 20-21.7mg/kg.(91, 95) The neurotoxic dose for cats is 3.8mg/kg, and the fatal dose is 18.4mg/kg.(96) The toxic effects on the myocardium seem more difficult to treat successfully than for other local anaesthetics, and the more concentrated solutions (0.75%) had a higher rate of toxic complications.(84, 89) Bupivicaine is often combined with lidocaine to provide a mixture with the quick onset of action from the lidocaine and a long length of action from the bupivicaine.(15, 89, 90) There is no published data supporting this beneficial effect of the mixture and there may be a comparable onset of action time between lidocaine and bupivicaine.(88) Significant changes of the individual drug's pH will occur upon mixing and this will likely alter their efficacy *in vivo*. Bupivicaine is almost exclusively used as a local infusion, but there has been one study in rabbits showing that topical 0.75% bupivicaine was as effective as topical 0.5% tetracaine in producing corneal anaesthesia.(98)

Mepivicaine

Mepivicaine's onset of action is 3 to 5 minutes, and it has a duration of 45 to 150 minutes.(15, 20, 86) Mepivicaine is thought to be less of an irritant to local tissues than lidocaine, potentially due to its slightly lower pka of 7.6, although it has an equivalent potency.(17, 83) The mean cumulative lethal dose in dogs is 80mg/kg.(91) Currently there are no published dosages for cats or dogs, though a dose from an online site is 5mg/kg for dogs and 2.5mg/kg in cats.(18) Due to its similar potency to lidocaine, the lidocaine dosing recommendations could be used as a guide.

Proxymetacaine (Proparacaine)

This topical anaesthetic drug has a very rapid onset of approximately 10 seconds, and in dogs has a significant anaesthetic effect for 45 minutes with a maximal effect lasting 15 minutes.(15, 83, 99) This can be extended out to a length of effect of 55 minutes and a length of maximal activity of 25 minutes with a second drop after one minute.(99) Proparacaine is less irritating that topical tetracaine and the concentration for maximal effect is 0.5%.(15, 82, 100) This drop

is best stored refrigerated as its activity begins to reduce after two weeks stored at room temperature.(101)

Tetracaine (Amethocaine)

Topical tetracaine has a rapid onset of approximately 15 seconds and provides topical anaesthesia of 10 to 20 minutes.(15, 81, 82) Tetracaine tends to be more irritating than topical proparacaine, causing a significant reddening of the conjunctiva after application.(81) The concentration for maximal effect is 1%.(15)

Oxybuprocaine (Benoxinate hydrochloride)

This topical drug has very similar characteristics to proparacaine and tetracaine as a 0.4% solution, providing corneal anaesthesia within 1 minute of application and a duration of 15-50 minutes.(102) Oxybuprocaine appears to be less irritant tetracaine, with a lower occurrence of conjunctival hyperaemia after application in dogs in one study.(102)

Additives used for local anaesthesia

A multitude of different additives have been combined with local anaesthetic agents to enhance their effect. The additives and their effects are listed below.

Hyaluronidase

Hyaluronic acid is a large glycosaminoglycan that fills much of the interstitial space, and is thought to provide significant resistance to diffusion through tissue of an injected solution.(15) Hyaluronidase is an enzyme that increases the tissue permeability to injected fluids by breaking down hyaluronic acid, but it does not affect the capillary permeability or fascial barriers.(15, 103) Hyaluronidase shortens the onset and duration of action of local anaesthetics, and due to its effect on drug diffusion, may enhance extraocular muscle blockade and eyelid akinesia.(15, 104) However, hyaluronidase does not appear to affect the quality of local anaesthetic orbital block at 10 minutes after infusion when compared to groups without hyaluronidase.(105-107) Hyaluronidase may be most beneficial with peribulbar regional anaesthesia techniques, as the solution has a greater distance to diffuse than for an intraconal block.(103, 108) Complications are rare but there is a potential link between use of hyaluronidase and orbital swelling associated with either infection, pseudotumor, or an allergic reaction.(103, 109) The interstitial space normalises in its structure within 24 to 48 hours of hyaluronidase infiltration, as new hyaluronic acid is formed.(15) Hyaluronidases' effect on

shortening the time of onset of local anaesthetic blocks may be significantly beneficial in human theatre situations where patients are not anaesthetised and the surgeons have a large theatre list, however the slight speed benefit is unlikely to be significant or beneficial in a veterinary ophthalmic surgical situation.

Bicarbonate

Addition of sodium bicarbonate to local anaesthetic agents alkalises the solution and increases the membrane penetration of the drug by favouring conversion of the local anaesthetic to the more lipid soluble tertiary form.(15, 89, 103, 110, 111) This may shorten the onset time and result in less pain upon tissue infiltration.(15, 103, 110, 111) However, increasing the pH can cause an increased failure rate of the block and precipitation may occur if too much bicarbonate is added.(89)

Epinephrine (Adrenaline)

Epinephrine is an α and β adrenergic agonist that has a wide variety of systemic effects.(81) Only those effects pertaining to its use as an adjunct to local anaesthetic injections will be discussed here. Epinephrine has been used with local anaesthetics for its vasoconstriction effects that may reduce the local drug clearance, prolonging the length of activity and counteracting the vasodilatory effects of infused local anaesthetics.(81, 103, 112) A solution diluted to 1:200000 will cause vasospasm and slow the drugs absorption systemically, causing the length of action of short acting local anaesthetics to be prolonged.(15) However, this effect is short lived as the epinephrine is rapidly inactivated by catechol-0-methyltransferase, with the vasoactive effects lasting only around 20 minutes.(17) In addition, vasoconstriction has not been shown to reliably prolong the length of action of an infused local anaesthetic.(15, 108) Epinephrine's effects on the cardiovascular system can stress the heart by increasing the heart rate, systolic blood pressure and the risk of arrhythmia.(15, 81) With the lack of clinical benefits of adrenaline as an additive, and the risk of causing cardiac stress, routine usage of adrenaline in local anaesthetic infusions should be avoided.

Other additives

Additional drugs have been investigated for inclusion in solutions for regional anaesthesia and nerve blocks. Medetomidine prolonged the motor and sensory block produced in dogs in one study through an unknown peripheral mechanism of action.(86) Clonidine has been shown to

extend the length of action for globe anaesthesia and globe and eyelid akinesia.(103, 113) Using a long-acting local anaesthetic like bupivicaine may provide the prolonged anaesthesia desired, without having to combine different drugs. Neuromuscular blockade agents like rocuronium, atracurium and vecuronium have some topical activity in vitro and have been shown to improve globe akinesia when added to peribulbar blocks in humans.(103, 114-117) The risk of intrathecal injection of these agents is unknown, but they could cause severe neurological dysfunction.(118-120) The benefit of adding neuromuscular blockade agents to a local anaesthetic solution can be overcome by using an intraconal block technique rather than an extraconal/peribulbar, as is discussed later.

Ocular neuroanatomy pertinent to local anaesthetic techniques

Knowledge of the location and function of the nerves involved in and around the eye is essential for performing effective local and regional anaesthesia. Nerves that traverse the orbit can be classified as either intraconal or extraconal. Intraconal nerves are within the interior of the extraocular muscular cone, whereas extraconal nerves are exterior to the extraocular muscle cone (Table 1.). Orbital local anaesthetic techniques deposit the drug either intraconally (retrobulbar or sub-Tenon's blocks) or extraconally (peribulbar block). The extraocular muscle cone provides an incomplete barrier to the spread of local anaesthetic.(121-123) As most of the nerves that require anaesthesia for globe surgery are located within the muscular cone, a technique that delivers drug to the intraconal region is required for an effective block. The exception to this is the dorsal oblique muscle, which has an extraconal insertion of the trochlear nerve in the muscle, and may not be paralysed by retrobulbar injection.(3, 123-125)

Sensory innervation is provided by the ophthalmic branch of the trigeminal nerve, via the terminal branches as the long and short ciliary nerves.(1, 90) Nociceptive information is relayed in a pathway that includes c and Aδ trigeminal sensory fibres, the dorsal horn of the medulla, the thalamus and the primary somatosensory cortex.(126, 127) Upon exiting the cranial vault through the orbital fissure, the ophthalmic nerve branches and the nasociliary nerve traverses the ciliary ganglion near the apex of the extraocular muscular cone and continues rostromedial to the optic nerve towards the globe. Here it branches further into the short ciliary nerve and long posterior ciliary nerve (Figure 1).(1, 2, 90) These ciliary nerves

penetrate the globe adjacent to the optic nerve, with the short ciliary nerve providing sensation to the posterior segment, and the long ciliary nerve continuing anteriorly in the suprachoroid at three and nine o'clock locations on the globe. This sends sensory branches out to ciliary body, iris and finally cornea.(1, 82) Corneal nerves penetrate the limbus and extend to the corneal centre as 10-14 major stromal nerves at the level of the mid-posterior corneal stroma. These stromal nerves branch repeatedly as they move anteriorly to form the sub-epithelial nerve plexus, a highly anastomotic plexus immediately below the stromal-epithelial interface. Axons from the sub-epithelial nerve plexus penetrate the epithelial basal lamina and give rise to the sub-basal nerve plexus, which terminates as free nerve endings in the wing cell layer in the corneal epithelium.(128-130) Peripheral (perilimbal) cornea is innervated by several smaller nerve fibres that penetrate the limbus at the sub-epithelial level for 2-4mm at various sites encircling the cornea, terminating in the corneal epithelial wing cell layer.(128) Corneal sensitivity varies between species, and also within species with varied breed conformation.(128, 129, 131) Most notably, brachycephalic dogs and cats have reduced corneal sensitivity and nerve fibre density compared to dolichocephalic dogs and domestic short haired cats.(128, 129) This may influence the severity of corneal pathology that brachycephalic breeds are prone to.

The ciliary nerves can be blocked as it passes through the retrobulbar cone, or in the sub-Tenon's space with diffusion through sclera.(90) Extraconal sensory nerves may not be blocked with retrobulbar techniques, so there may be retention of sensation in the peripheral conjunctiva with intraconal anaesthesia.(2, 124)

The oculocardiac reflex is of specific interest to ophthalmic surgeons. It is a reflex defined as a reduction of the patients heart rate of 20% or more in response to ocular manipulation.(15, 132) The afferent arm of this reflex involves the trigeminal nerve and the efferent arm involves the vagus nerve, with its effects on the myocardium.(133) The oculocardiac reflex is most reliably initiated by traction on the medial rectus and inferior oblique extraocular muscles, but can be initiated by any intense ocular surgical manipulation, particularly during enucleation.(15, 132-135) If severe, this reflex can result in marked bradycardia, development of arrhythmias, and cardiac arrest.(15, 133) Treatment for this bradycardia involves systemic atropine, retrobulbar local anaesthesia and increasing ventilation via a ventilator or intermittent positive pressure ventilation.(15, 135) Prevention of this reflex can be achieved by

preoperative treatment with atropine, or regional local anaesthesia.(15, 74, 76, 136) One study in dogs showed that atropine treatment abolished the bradycardia, but enhanced the duration and severity of respiratory depression.(137) Therefore atropine treatment is not without risk. There are some reports of this reflex in the veterinary literature: one dog with a choroidal tumour that extended into the orbit, one foal undergoing cataract surgery, and a group of horses undergoing a variety of ocular surgeries.(135, 136, 138) A recent study assessed the impact of the oculocardiac reflex in response to globe compression in conscious dogs and rabbits. This suggested that the reflex is of little clinical importance in dogs, as the reduction in heart rate was not enough to concern a healthy dog, however blood pressure changes were no measured.(133)

Figure 1: Lateral aspect image illustrating the spatial anatomy of nerves of the eye and orbit, from Miller's anatomy of the dog.(1)

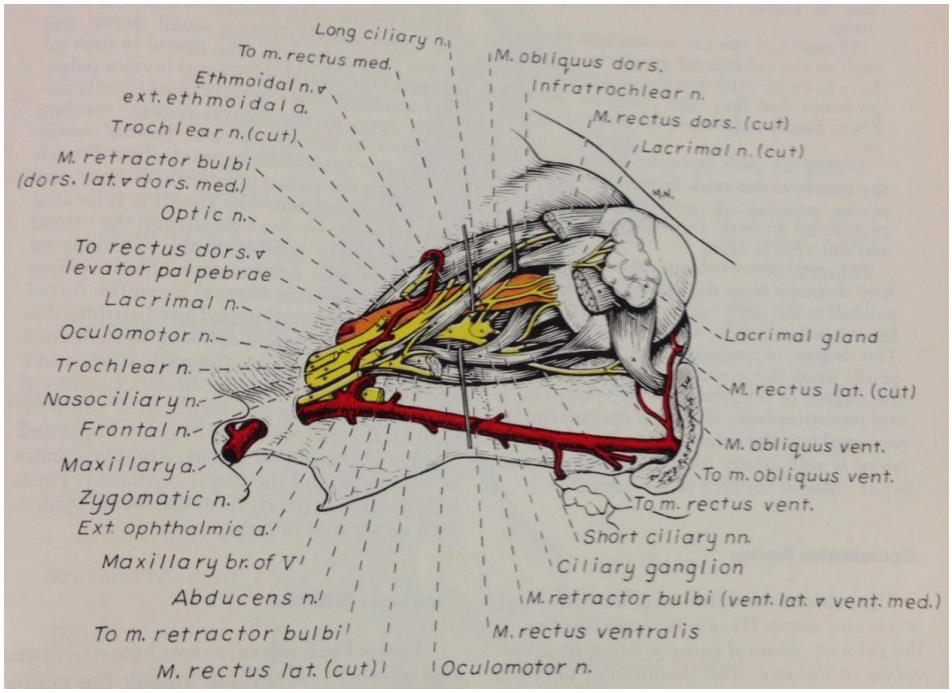


Table 1: Anatomical and functional characteristics of the nerves pertinent to ocular local anaesthesia techniques.(2, 3)

Nerve	Innervation	Anatomic location	Action
Optic (Cranial nerve II)	Retina	Intraconal	Sensory (vision)
Oculomotor (Cranial nerve III)	Most extraocular muscles including: Dorsal, Medial and Ventral rectus, and Ventral oblique.	Intraconal	Motor (globe movement)
Trochlear (Cranial nerve IV)	Dorsal oblique extraocular muscle	Extraconal	Motor (globe movement)
Trigeminal (Ophthalmic and Maxillary branches of Cranial nerve V)	Orbit, globe, and eyelids	Varies dependent on the branch	Sensory (entire face)
Abducens (Cranial nerve VI)	Lateral rectus and Retractor bulbi extraocular muscles	Intraconal	Motor (globe movement)
Facial (Cranial nerve VII)	Orbicularis oculi muscle	Superficial lateral head	Motor (eyelid movement)
Sympathetic nerves	Iris dilator muscle, orbital smooth muscle, levator palpebrae superioris muscle	Superficial lateral head	Motor (globe positioning, nictitans position, pupillary control, and upper lid retraction)
Parasympathetic nerves	Iris sphincter muscle	Intraconal	Motor (pupillary control)

Ocular soft tissue anatomy pertinent to local anaesthetic techniques

The intraconal space is contained within the extraocular rectus muscles, with the annulus fibrosis posteriorly and the caudal globe anteriorly.(123) Septa within the cone support the vascular structures, but the region is not completely closed off from the rest of the orbit as the junctions are incomplete.(121-123) This allows solutions to essentially diffuse freely

throughout the orbit via compartments of loose fatty tissue, the corpus adiposum.(123) Many major structures reside within the extraocular muscle cone including: optic nerve and meningeal coverings, most of the arteries that supply the orbit, and nerves that provide autonomic, motor and sensory innervation to the globe.(3)

The rectus muscles originate from the annulus fibrosis at the apex of the orbital cone.(123) The dorsal oblique muscle originates from the anteromedial to the optic canal, and the ventral oblique muscle uniquely originates from the rostro-ventral orbit.(123) All of the extraocular muscles insert onto specific regions on the sclera rostral to the equator.(82)

Tenon's capsule, also referred to as fascia bulbi, is a fibroelastic layer that surrounds the entire scleral portion of the globe from the corneal limbus to the optic nerve.(3, 90, 139) It allows for smooth globe rotation and delineates the sub-Tenon's space, also known as the episcleral space.(3, 121, 139) Near the equator, Tenon's capsule is perforated by the insertion tendons of the extraocular muscles before they insert on the sclera, and this site of muscle perforation separates the anterior and posterior portions of sub Tenon's space.(3, 90, 125) Anteriorly Tenon's capsule fuses with the bulbar conjunctiva before they both insert at the limbus.(3, 125, 140) There are other Tenon's capsule membranes that extend to the palpebral conjunctiva, tarsus palpebrae and orbital septum.(140)

The main arterial supply to the eye and orbit is from the ophthalmic artery, a branch of the internal carotid.(123) This vessel passes into the orbit though the optic canal within the meningeal sheath, and it perforates the sheath as soon as it enters the orbit.(123) It continues to branch to supply the orbital structures, though in humans a branch runs anteriorly above the medial rectus.(123) In dogs, the major arterial branches are in the ventral and ventromedial orbit (Figure 2).(1, 141) The globe is supplied by two or four long posterior ciliary arteries, which pass through the superficial sclera at 3 and 9 o'clock on the globe, accompanied by the long posterior ciliary nerves.(1, 82, 141) Numerous short posterior arteries penetrate the sclera 3-5 mm from the optic nerve, and provide blood supply to the choroid and iris.(1, 82) It is worth noting that dogs lack the central retinal artery and vein that is present in humans, and don't have the associated complications with high volume orbital injections.(82, 142)

In dogs there are usually four vorticose veins that drain venous blood from the globe. These emerge from the sclera near the equator in between the insertions of the rectus muscles and closely follow the posterior globe curvature.(1, 82) There are two main orbital venous drainage channels in dogs: the supraorbital vein (dorsal external ophthalmic vein), and the inferior orbital vein (ventral external ophthalmic vein) which anastomose posterior to the globe (Figure 3).(1, 82) These veins exit the orbit via the facial vein, cavernous sinus and maxillary vein, or the deep facial vein.

In dogs, the size of the orbit varies with the breed with skull size and conformation. Principally dolichocephalic breeds have very deep orbits, while brachycephalic breeds have much shallower orbits. The exact orbital volume of a different dog breeds has not been determined.(141) The globe dimensions have less variation between breeds and are approximately 20-25mm anterior-posterior, 18.7-25mm vertically, and 19.7-25mm horizontally.(141)

Figure 2: Lateral aspect of the orbit illustrating the extraocular muscles and arteries, from Miller's anatomy of the dog.(1)

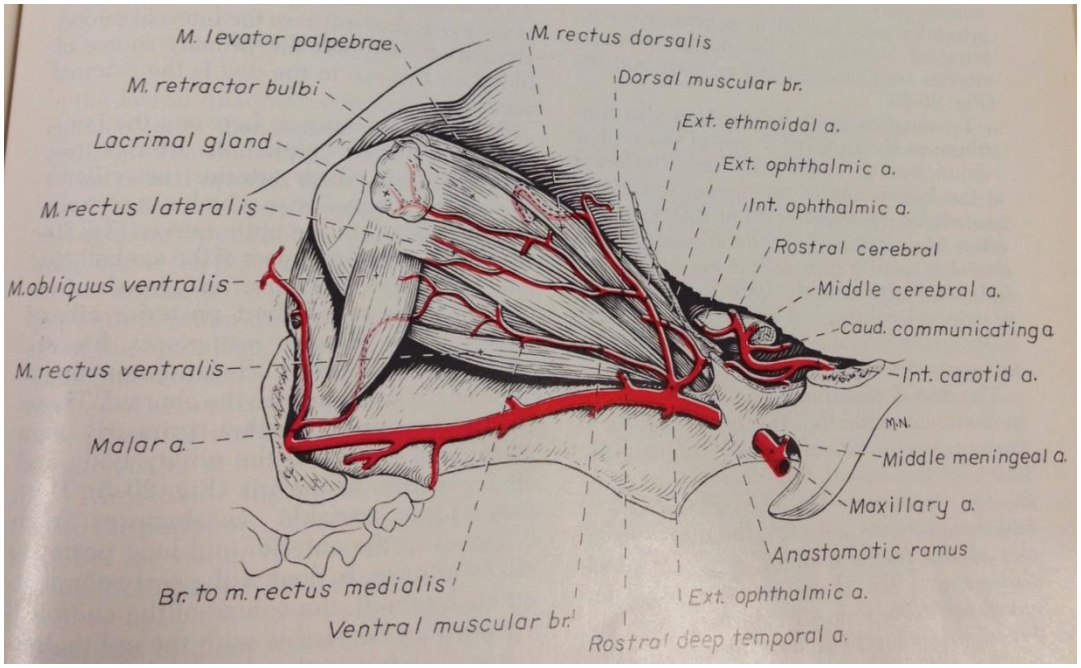
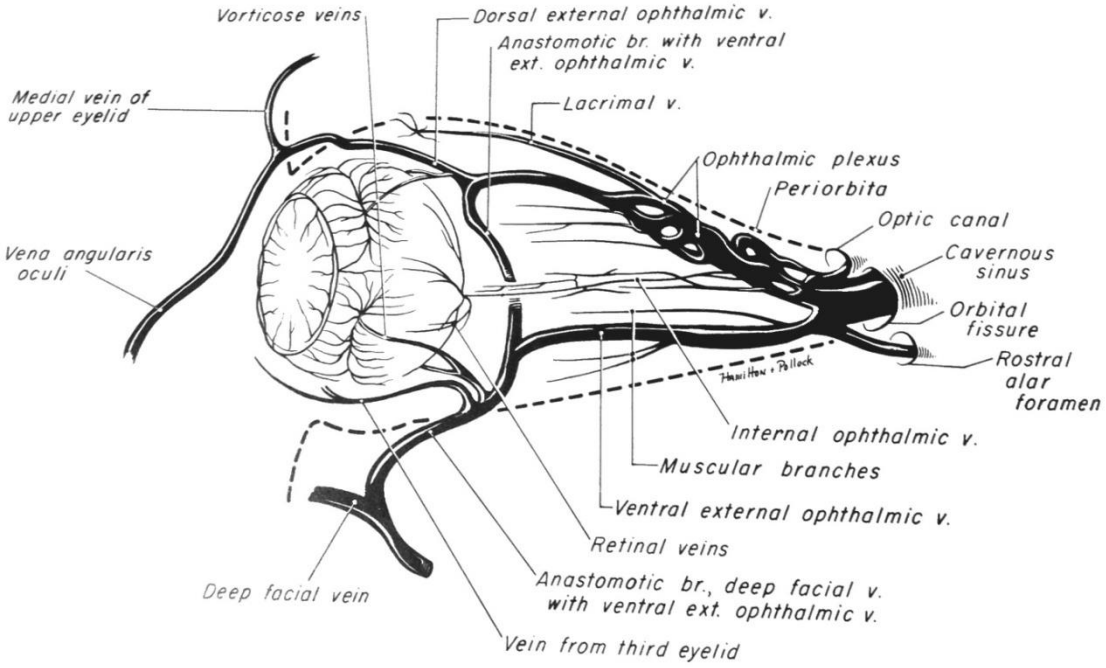


Figure 3: Venous drainage tracts of the globe and orbit, from Miller's anatomy of the dog.(1)



Current techniques and applications in human ocular local and regional anaesthesia

Human ophthalmic surgeons have embraced and advanced techniques that provide localised anaesthesia and have applied it to a variety of ocular procedures. The details of the different techniques with their advantages, disadvantages and complications are described below.

Topical anaesthesia

There are a surprising variety of procedures than can be performed under topical anaesthesia. Basic lid procedures have been performed after applying a topical anaesthetic cream (EMLA).(59) Topical tetracaine is commonly used to desensitise the cornea to allow diagnostic testing, foreign body removal, and has also been used as an adjunct to regional blocks.(15, 81) Cataract surgery can also be performed under topical anaesthesia.(61) This technique is short acting, does not provide globe or lid akinesia and may not provide complete anaesthesia in all cases.(143-148) It is reported that a gel formulation is more successful than an aqueous drop

and that superior analgesia is achieved when it is combined with intracameral local anaesthetic to anaesthetise the iris.(3, 97, 143)

Superficial infiltrative anaesthesia

Local anaesthetic infiltration has been used to perform minor lid surgery in conscious patients.(149) Occasionally a facial nerve block is used in addition to a retrobulbar block to prevent the blink reflex during surgery.(3, 89) There are a variety of techniques described in humans (van Lint block, Atkinson block, O'Brien block and Nadbath block) that are related to the level of the nerve tract where the block is performed.(89)

Orbital anaesthesia

Orbital anaesthetic techniques are the most important local anaesthetic blocks used in human ophthalmic surgery. These anaesthetic blocks allow complicated ocular surgery to be performed including: cataract surgery, vitreoretinal surgery, and strabismus surgery.(61, 70, 150) These procedures are often performed without general anaesthesia. Anaesthetising the orbital contents provides a desensitised, immobile eye that is suitable for surgery. The anaesthetic techniques used to achieve orbital anaesthesia can be divided into three types: retrobulbar, peribulbar and sub-Tenon's. The advantages, disadvantages and risks associated with each technique are discussed below.

Specific orbital anaesthesia techniques in human ophthalmology

Retrobulbar block

A retrobulbar block involves the injection of a local anaesthetic into the extraocular muscle cone, resulting in an intraconal block. To achieve this, a long curved needle is introduced into the orbit to penetrate the extraocular muscle cone and deposit 3-5ml of local anaesthetic behind the globe.(3) There are a variety of different injection techniques used in humans, the discussion of which is beyond the scope of the paper. The appeal of this technique is the targeted delivery of the local anaesthetic within the extraocular muscle cone, which results in globe akinesia and anaesthesia. The disadvantages of this technique revolve around the fact that a sharp needle is being blindly passed into the intraconal space, where it can traumatise a variety of important structures. The most significant post-injection complications include: globe perforation, retrobulbar haemorrhage and brain-stem anaesthesia. Many studies report the complication rates from retrobulbar anaesthesia and their findings vary considerably (Table 2.). One large study found that sharp needle techniques (retrobulbar and peribulbar

injection) had a 2.5x higher risk of serious complications when compared to a blunt cannula technique (sub-Tenon's anaesthesia).(61)

Brain-stem anaesthesia is a potentially life threatening complication from retrobulbar injection, typically caused by subdural (intrathecal) injection through the optic nerve sheath.(151) A second potential mechanism is an intra-arterial injection that causes retrograde flow though the ophthalmic artery, followed by normograde flow though the internal carotid artery to the brain.(151, 152) This is thought to lead to immediate signs of anaesthesia when compared to subdural injection where there is typically a delay.(153, 154) The local anaesthetic effects on the brain include: drowsiness, blindness of the contralateral eye, abnormal shivering and vomiting; through to the more severe signs of respiratory depression, apnea, hemiplegia, aphasia, convulsions, unconsciousness and cardiopulmonary arrest.(151, 155) The treatment for brain-stem anaesthesia is supportive care until the drug effects wear off; with respiratory ventilatory support, cardiovascular support and anti-seizure therapy if neurological signs are present.(156) Injection techniques that deposit local anaesthetic close to the apex of the orbital cone are the highest risk for this complication as in this region the optic nerve is quite immobile and less likely to be deflected away from a needle tip.(3) This is the reason that the rate of complications are quite dependent on the retrobulbar injection technique used.(153)

Globe perforation with retrobulbar injection typically occurs in highly myopic eyes that have a long axial length or a myopic staphyloma as the curved needle is prematurely directed axially, perforating the globe. Patients that have previously had a scleral buckling surgery for retinal detachment have more scar tissue present, which can deviate the needle toward the globe.(3, 157-159) To preserve vision in these patients, prompt diagnosis and referral to a Vitreoretinal surgeon is required.(3)

Retrobulbar haemorrhage can occur with any needle introduction into the orbit, but the highest risk anatomic region is around the orbital cone apex where the ophthalmic artery enters the orbit.(123) Severe haemorrhage can indirectly increase the intraocular pressure and cause exophthalmos.(109) Most retrobulbar haemorrhages are minor and treated by compression, however if it and arterial bleed and causing significant pressure on the optic nerve and retinal vessel, surgical decompression of the orbit is indicated.(15, 109)

Introduction of fluid into the orbit can compress the globe, cause an elevation in the intraocular pressure, and increase the complication rates during cataract surgery. In addition, high volume orbital injections can potentially decrease vascular flow, and compromise the optic nerve and retinal blood supply.(142, 160) Pressure increases are associated with higher injection volumes.(161-164) Compression of the globe after injection has been advocated to help reduce the intraocular pressure before surgery. This theoretically increased aqueous outflow by opening up the iridocorneal angle, but this compression can cause very high intraocular pressures with peaks of 400mmHg.(165, 166) More recent studies have shown that the intraocular pressure rise after orbital injection dissipates on its own with time.(161-163, 167)

Table 2: Occurrence rates of severe complications associated with retrobulbar injection from a variety of references.

Reference	Life threatening	Sight threatening	Brainstem anaesthesia	Globe perforation	Severe Retrobulbar haemorrhage	Cardiac complications
(4)	1.8 per 10000			1.4 per 10000	4.2 per 10000	
(9)		68 per 10000	5 per 10000	10 per 10000	52 per 10000	
(168)			7 per 10000	1 per 10000		
(109)			30-80 per 10000	7.5 per 10000	1-300 per 10000	
(158)					10-170 per 10000	
(153)			20 per 10000			
(156)			20-33 per 10000			
(5)	1.5 per 10000	4.5 per 10000				
(61) (Sharp needle techniques)					8 per 10000	3.6 per 10000

Peribulbar block

A peribulbar block involves using a short fine needle to inject local anaesthetic into the orbit. There are many different techniques, however the main principles involve a needle no longer than 25mm in length, with a 25G or narrower calibre inserted in one or more injections sites.(3) This is an extraconal block and is effective due to the fact that the orbital septa are not complete, and hence fluids can diffuse freely between the extraconal and intraconal regions. A relatively large volume of 6 - 12ml is used to ensure adequate diffusion of the drug through the

corpus adiposum, into the extraocular muscle cone and up into the lids.(3) This technique was developed to help avoid the previously stated risks associated with retrobulbar injection. This is largely because needle insertion is limited to 25mm, and therefore the risk for traumatising intraorbital structures is lower.(3, 121, 125) Disadvantages of this technique are that a high volume of local anaesthetic is required which can affect the intraocular pressure as previously stated, and this technique may require additional injections to achieve full anaesthesia and akinesia due to relatively imprecise deposition of local anaesthetic.(121, 125) Although the risk may be lower, peribulbar injections can still result in globe perforation in 0.6-1.4 cases per 10000 , retrobulbar haemorrhage in 4.2 per 10000 cases, brain stem anaesthesia is reported in one case, and minor complications are reported in 182 per 10000 cases.(4, 61, 109, 154)

Sub-Tenon's block

The first description of sub tenons space anaesthesia for enucleation was by Turnball, who instilled cocaine after opening tenons capsule.(14) The first in depth description of sub-tenons anaesthesia and its application for cataract surgery was much later.(125) Currently this is the most common block technique used in many centres around New Zealand and the United Kingdom.(150) After surgically disinfecting the globe and conjunctiva, a small incision is made in the bulbar conjunctiva, tenons capsule is dissected through to the level of sclera. A blunt, curved cannula is then inserted so the tip sits posterior to the globe equator, and 3-5ml of local anaesthetic is infused into the sub-Tenon's space.(90, 125, 163) This results in local anaesthetic being deposited within the extraocular muscle cone and hence produces an intraconal block without requiring the passage of a sharp needle.(125) The rationale for this anaesthetic block technique is to avoid the risk of retrobulbar haemorrhage, globe perforation, optic nerve damage, and intrathecal injection, while still providing prolonged and reliable anaesthesia.(125) In humans the dissection and infusion is most commonly performed though the ventromedial bulbar conjunctiva.(125) This intraconal block produces globe akinesia and anaesthesia and, with higher volumes, diffusion into the periorbital tissues and lid akinesia.(9, 90, 169-171) Sub-Tenons block has been shown to provide more effective anaesthesia than a peribulbar lock or topical anaesthesia for vitreoretinal and cataract surgery.(121, 144, 146, 160) This technique combines the best characteristics of the other orbital block techniques, with a lower rate of severe complications (Table 3). The complications associated with sub-Tenon's anaesthesia are summarised in table 4. The risk of severe complications is less than with sharp needle techniques, but the risk of mild complications with sub-Tenon's anaesthesia including chemosis and subconjunctival haemorrhage is 2.3x higher.(5, 9, 61) Globe

perforation can occur with sharp dissection of tenons capsule hence blunt dissection should be used.(90, 172) The highest risk patients for globe perforation are those that have scarring from previous surgery.(109) Similarly the most likely cause for central nervous system spread of local anaesthetic after sub-Tenon's infusion is if the optic nerve dural sheath has been snipped by the tip of the scissors during sharp dissection.(172) There has been one reported death associated with sub-Tenon's anaesthesia which was considered to be due to the severe cardiac disease present, rather than the technique or drug.(173)

Table 3: Occurrence rates of severe complications with different orbital local anaesthetic techniques(4, 5)

Local anaesthetic technique	**Number of cases**	**Reported incidence of life threatening complications (95% CI)**	**Reported incidence of sight threatening complications (95% CI)**
Peribulbar	42700	3.5 per 10000	8.2 per 10000
	114750 (estimate)	0.7 per 10000	2.9 per 10000
Retrobulbar	11000	1.8 per 10000	5.6 per 10000
	13125 (estimate)	1.5 per 10000	4.5 per 10000
Sub-Tenons	4380	0	0
	159750 (estimate)	0.6 per 10000	0.6 per 10000
Topical	1870	5.4 per 10000	0
	37125 (estimate)	0	0

Table 4: Occurrence rates of severe and minor complications associated with sub-Tenon's anaesthesia from a variety of references.

Ref.	Retrobulbar or severe subconjunctival haemorrhage	Brainstem anaesthesia or other neurological affect	Globe perforation	Orbital cellulitis	Mild chemosis or mild subconjunctival haemorrhage	Intraocular haemorrhage	Vision loss	Extra-ocular muscle damage	Cardiac or respiratory effects
(90)					4000 per 10000				
(174)					5200 per 10000				
(5)	0.1 per 10000	0.4 per 10000	0.1 per 10000	0.2 per 10000		0.1 per 10000		0.1 per 10000	0.2 per 10000
(175)					330 per 10000				
(172)		1.4 per 10000	1.4 per 10000			2.8 per 10000	1.4 per 10000		
(176)								1 case	
(177)				1 case					
(178)				1 case					
(9)	1.6 per 10000				1260 per 10000				
(61)	1.9 per 10000				532 per 10000				2.3 per 10000
(4)	<2.3 per 10000		<2.3 per 10000						

Current applications of local anaesthesia in veterinary ophthalmology

There are few reports of local anaesthesia being used in veterinary ophthalmic surgery. The established techniques, benefits and complications are discussed below.

Topical anaesthesia

Topical anaesthesia is commonly used as a diagnostic aid to desensitise the cornea and conjunctiva, facilitating the examination of painful eyes and allowing diagnostic testing.(82) Some simple surgical procedures can be performed in compliant animals under topical anaesthesia including: superficial corneal foreign body removal; indolent ulcer therapy in the form of corneal epithelial debridement, grid keratotomy, punctate keratotomy, or corneal burring for indolent ulcers; conjunctival pedicle graft transection; and conjunctival biopsy.(82) Topical anaesthesia maybe used as an adjunct to general anaesthesia for surgery of the lids and cornea, being applied immediately before and after surgery. The value of this approach is

questionable due to the very short length of action of the currently available topical anaesthetics and the likely lack of lid anaesthesia.

Topical opioids have been investigated as an analgesic to treat pain from corneal ulceration.(34, 179) One study using topical nalbuphine (a synthetic mixed agonist opioid) showed it was of no benefit, with four out of five cases in the nalbuphine group requiring rescue analgesia.(34) Another study assessing topical morphine demonstrated a benefit in controlling corneal pain.(179) An important consideration for using topical medication in cases with a corneal ulcer is whether the medication has any deleterious effect on the corneal healing. It is well known that topical local anaesthetics are epitheliotoxic and retard corneal healing, and thus are contraindicated for therapeutic use with corneal ulceration. There is some evidence that topical morphine sulphate has no deleterious effects on corneal healing, potentially making it an option for therapeutic use in the presence of corneal ulceration.(179, 180)

Regional anaesthesia for lid surgery

Local anaesthetic infusion after lid surgery has been used to provide improved post-operative analgesia in dogs in one study.(181) The local anaesthetic was infused adjacent to and through the surgical site, after the wounds were closed in a variety of eyelid surgeries. It was also used in combination with a retrobulbar and subconjunctival block for enucleations in the same study. A mixture of lidocaine and bupivicaine was used with 1-3ml infused per eye, up to a maximum dose of 5mg/kg of lidocaine, and 1.5mg/kg of bupivicaine. Dogs that received this adjunct regional anaesthesia subjectively have smoother recoveries, though no objective pain scoring or other assessment was made and further studies would be required to test this benefit.

A technique was described that used topical anaesthesia and a regional conjunctival local anaesthetic infusion to place a nictitans flap to treat corneal ulceration in a group of dogs.(60) Topical anaesthetic was used to desensitise the conjunctival surface; then 2% lidocaine was used to perform an auriculopalpebral nerve block for lid akinesia, infused under the nictitans conjunctiva and dorsolateral bulbar conjunctiva. This avoided general anaesthesia in these patients with significant senility, hepatic, cardiovascular, and renal disease.(60) Local anaesthetic regional infusions are used much more commonly in large animal species, often in combination with sedation for eyelid and nictitans surgery.(62, 63) Facial nerve blocks are

often needed in horses for lid akinesia to allow examination of the globe, due to strong orbicularis oculi muscle action in this species.(182, 183)

Intracameral local anaesthesia

In one small study, 0.3ml of 2% lidocaine was injected into the anterior chamber 10 minutes before starting phacoemulsification cataract surgery in dogs.(78) The study found that the isoflurane requirements were lower than for the control group, and that the length of time post-surgery before systemic analgesia was required was shorter in the control group. The reduction in analgesic requirements in the treatment group were thought to be due to the prevention of central nociceptive stimulation and the residual effects of the local anaesthetic post-operatively.

Orbital anaesthesia

Orbital anaesthesia is used much less commonly in veterinary ophthalmic surgery than in humans. This is likely because general anaesthesia is typically required for patient immobilisation, meaning globe specific anaesthesia is not a pre-requisite for surgery. However, the globe is rarely located in an appropriate position under general anaesthesia to perform ocular surgery without either fixation of the globe with clamps or suture, or paralysis of the extraocular muscles with systemic neuromuscular blockade agents.(82, 184, 185) Neuromuscular blockade agents are commonly used with general anaesthesia to perform cataract and lens luxation surgery to improve globe position and reduce the risk of intraoperative increased vitreal pressure with its associated complications.(186) These agents significantly affect the respiratory system causing respiratory depression at low doses, and respiratory muscle paralysis and apnoea at higher doses.(184, 185, 187, 188) Patients that have surgery under general anaesthesia without local anaesthetic have a higher requirement for anaesthetic gas, that has a dose dependent cardiopulmonary depressive effect.(78, 92, 189) As previously stated, general anaesthesia does not prevent nociception, and probably does not contribute towards intraoperative and post-operative pain management. Therefore, despite orbital anaesthesia not being absolutely essential to perform ocular surgery in most veterinary patients, there are potential benefits to using it as an adjunct to general anaesthesia.

Specific orbital anaesthesia techniques in veterinary ophthalmology

As is the case in humans, there are several different techniques to achieve orbital anaesthesia with local anaesthetics in animals. Each technique and its current application in veterinary ocular surgery is discussed below.

Retrobulbar injection

Retrobulbar injections are the most commonly used orbital anaesthesia technique in veterinary ophthalmology. There are many different techniques described that vary in their location of needle penetration and subsequent needle direction.(6, 56, 58, 62, 63, 92, 132, 136, 182, 190-195) The most recently described technique used in dogs is an inferiotemporal palpebral technique.(6) This technique involved using a 22G 1.5 inch spinal needle with a 20^{O} angle bend at the midpoint. The needle was positioned at the inferior orbital rim and inserted perpendicularly through the inferior lid at the junction of its middle and temporal thirds (Figure 4). The needle was advanced until a slight popping sound is detected, indicating piercing of the orbital fascia. The needle was then directed dorsonasally towards the apex of the orbit and advanced 1-2cm; then 2ml of 2% lidocaine was injected (Figure 5). This block technique did not show any increase in intraocular pressure or any other complication.

Pre-operative retrobulbar anaesthesia has been shown to be beneficial in controlling the post-operative pain in dogs that undergo enucleation surgery, with significantly fewer of the treated dogs requiring rescue analgesia.(30) Retrobulbar anaesthesia has also been shown to be beneficial in combination with general anaesthesia in horses undergoing enucleation, as horses that receive a retrobulbar block have a lower incidence of oculocardiac reflex.(132, 136) Retrobulbar injection can provide a central globe suitable for ocular surgery in horses, without requiring neuromuscular blockade and associated ventilatory support.(136, 184)

Retrobulbar anaesthesia combined with a ring block around the lids, an auriculopalpebral block and sedation can facilitate a standing enucleation approach in horses if general anaesthesia is contraindicated.(56, 194) This technique results in minimal haemorrhaging compared to recumbent horse enucleation and avoids the considerable risk to horses during recovery from general anaesthesia.(56, 64, 182) Standing enucleation techniques with retrobulbar anaesthesia are commonly used in cattle practice.(62)

Complications from retrobulbar injections are sparsely referenced in the veterinary literature, however extrapolation from humans can indicate the potential risk for similar types of complications occurring in animals. There is one well described case of brain-stem anaesthesia in a cat after a retrobulbar injection.(196) This cat received a mixture of lidocaine and bupivicaine, at a dose of 1.5 mg/kg and 0.75 mg/kg respectively, with a volume of 2ml. Post-injection apnea occurred which lasted for 45 minutes, and was treated with mechanical ventilation until spontaneous breathing occurred. During recovery it showed neurological signs that included tremors, nystagmus, and a lack of a dazzle reflex. The cat recovered fully after three hours of supportive care.

Many clinicians are reluctant to use retrobulbar anaesthesia for veterinary ophthalmic surgery due to the perceived and real risk of severe complications and the 'blind' nature of passing a sharp needle through tissue potentially causing unseen and unknown damage.

Figure 4: Photograph (rostral view) to illustrate the needle placement required for retrobulbar injection performed via the inferiotemporal palpebral technique and an anaesthetised dog.(6)

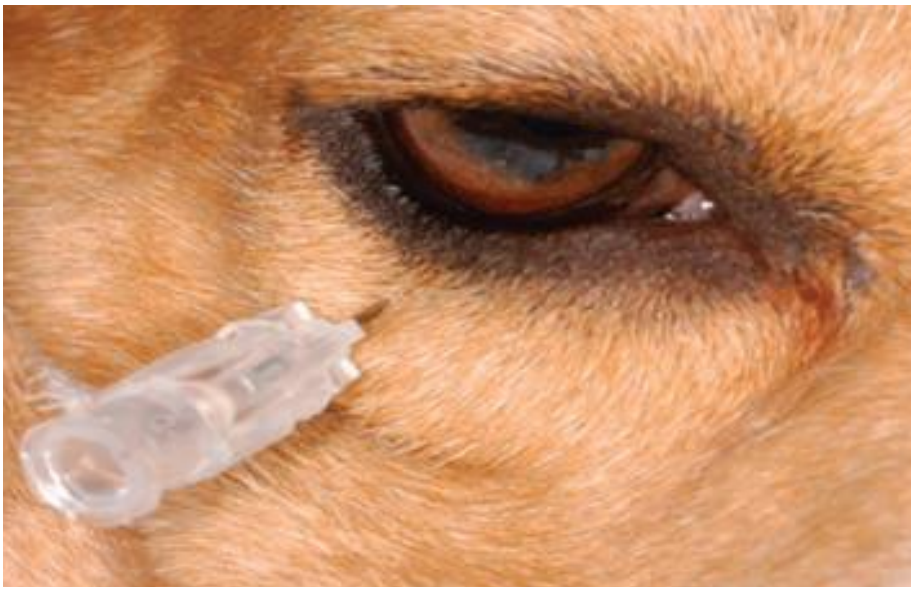
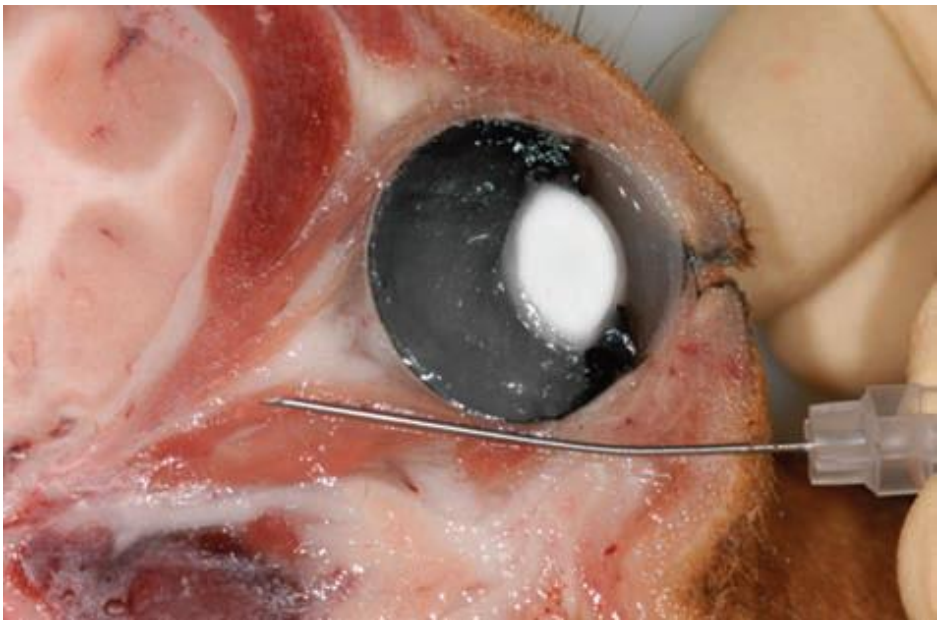


Figure 5: Photograph of a frozen canine skull that has been sectioned through an eye and orbit to illustrate the approximate path of needle placement for retrobulbar injection performed via the inferiotemporal palpebral technique. Note that the tip of the needle terminates in the intraconal fat.(6)



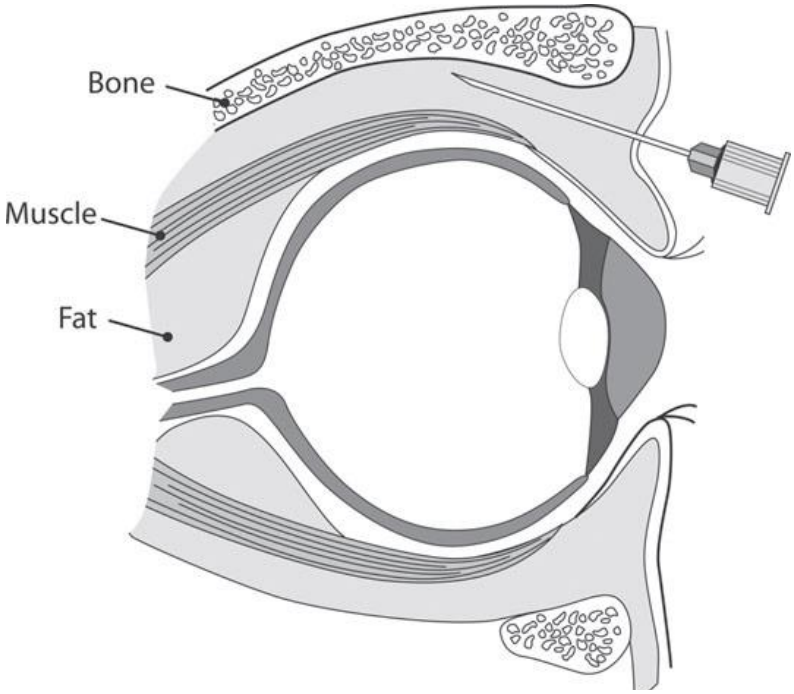
Peribulbar injection

Peribulbar (extraconal) injection of local anaesthetic for cataract surgery has been described infrequently in the veterinary literature; as a technique for cataract surgery in dogs, and as a preoperative block before enucleation in cats.(7, 197, 198) The technique used in the canine cataract study involved passage of the needle from the lateral globe region all the way through the orbit to contact the medial orbital wall, then an injection of 2ml of lidocaine was performed.(197) This needle pathway would create a relatively high risk for complications. Due to the poor experimental design, and imprecise and confounded reporting of effects of the peribulbar block, no real conclusions can be drawn from this particular publication.

Shilo-Benjamini et al initially assessed the effects of peribulbar block in cat cadavers, then later in experimental live cats, and the effects were compared to a retrobulbar injection.(7, 198) The peribulbar block was performed with a 25G 3/8 inch needle inserted trans-palpebral adjacent to the dorsomedial orbital wall and 3ml of solution was injected (Figure 6). The peribulbar block technique was shown to be more effective in distributing injectate into the intraconal region than the retrobulbar technique and provided equivalent post-injection corneal

anaesthesia. There was a significant, but transient, increase in intraocular pressure after peribulbar injection and the authors suggested that this may restrict its usage to cats that do not have glaucoma and or those not at risk of corneal perforation.(198) The elevation in intraocular pressure was probably associated with the higher volume required for peribulbar injection to ensure intraconal distribution, resulting in pressure on the globe in the fairly restricted orbital space in a cat.

Figure 6: Para-sagittal view of the eye and orbit showing technique for peribulbar injection at the dorsomedial site.(7)

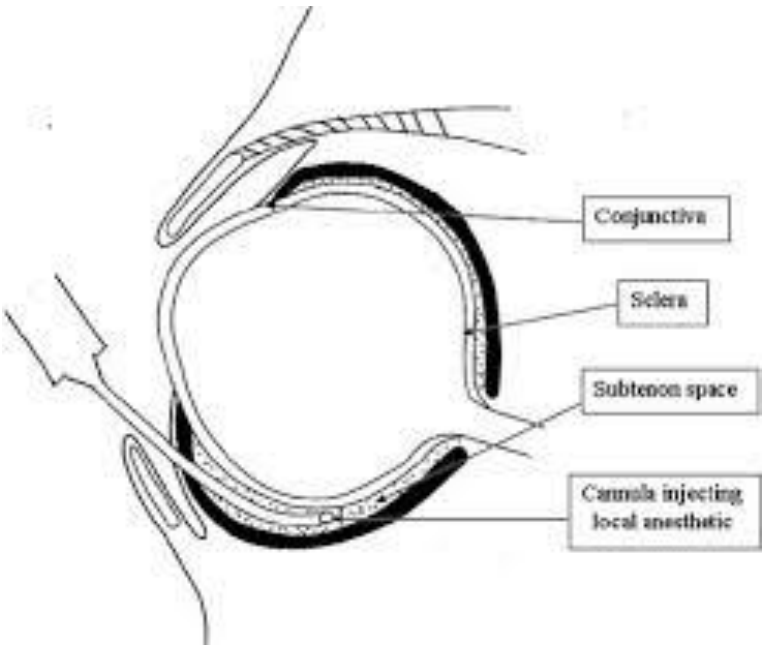


Sub-Tenon's block

Ahn et al has investigated the application of a sub-Tenon's block for cataract surgery in dogs.(189, 199) In one study, normal beagles were assessed for mydriasis and akinesia after either: sub-Tenon's anaesthesia (2ml 2% lidocaine), retrobulbar injection (2ml of 2% lidocaine), or systemic atracurium (0.2mg/kg IV).(199) Sub-Tenon's anaesthesia achieved mydriasis in nine out of ten eyes, compared to five out of ten eyes in the retrobulbar group. The onset of globe akinesia was shorter in the sub-Tenon's group than the retrobulbar group. The sub-Tenon's block was placed in the dorsomedial region, and there were no reported complications. In a second study, cataract surgery between groups of normal beagles (without cataracts) that either had a sub-Tenon's block (2ml 2% lidocaine), or systemic atracurium (0.2ml IV) with a 2ml

saline sub-Tenon's injection were compared.(189) They found greater mydriasis and better intraoperative analgesia in the sub-Tenon's group and no difference in the post-operative pain scores between the groups. Sub-Tenon's anaesthesia appears to be a good alternative to neuromuscular blockade in canine cataract patients. With neuromuscular blockade being non-essential, the associated negative respiratory effects would be avoided. The current data in dogs is restricted to these research dogs. Apart from not accurately representing the general canine population, they had cataract surgery performed without the dogs actually having cataracts. While this information shows promise in using sub-Tenon's anaesthesia for canine cataract surgery, an extensive clinical study is required to test its application for canine cataract cases. In addition, there may be other clinical applications for sub-Tenon's anaesthesia in veterinary ophthalmic surgery that may show benefits for corneal procedures or eye removal.

Figure 7: Diagrammatic example of placement of a sub-Tenon's cannula, and intraconal infusion of local anaesthetic.(8)



'Splash block' local anaesthesia

Orbital anaesthesia can be achieved using a 'splash block' technique after enucleation. Once the globe is removed, local anaesthetic is instilled into the orbit and/or over swabs placed to provide haemostatic compression prior to closure. Bupivicaine is commonly used due to its long length of action and appears effective, despite its reported slow onset of action. This is

possibly due to the orbital shape promoting retention of the bupivicaine after it is instilled, providing the required contact time for the drug to take effect. Anecdotally this significantly improves analgesia in dogs in the post-operative period when compared to enucleations that do not receive local anaesthesia (Personal communication R. A. Read). A study has recently been published comparing 'splash block' anaesthesia to retrobulbar injection for post-enucleation analgesia in dogs.(32) This study showed no significant difference in post-operative pain scoring between the two groups. However, there was a slight increase in pain scores through time in the splash block group, potentially either due to the post-incisional application of the block, or due to the reduced tissue retention of the drug compared to the injection technique.(32) This technique is quick and easy, however there is no benefit of improved intraoperative analgesia as the block is placed after the globe has been removed. A variant on this technique has been recently described where an absorbable gelatin haemostatic sponge soaked with a mixture of lidocaine and bupivicaine is placed into the orbit before closure.(31) This was compared to preoperative retrobulbar injection and the dogs were monitored with post-operative pain scoring. It was found that the soaked haemostatic sponges were as effective in providing post-operative analgesia as a retrobulbar injection, and the technique was simple to perform.

Conclusion

Orbital regional anaesthesia provides many desirable effects for ocular surgery. Sub-Tenon's anaesthesia is the newest technique used in humans and it has been shown to be very safe and effective. STB has potential to be a good option for canine ophthalmology, however an effective technique must first be developed.

CHAPTER 2

Canine Sub-Tenon's anesthesia technique

Introduction

The technique of STB is well established and described in human ophthalmology.(90, 125, 140, 169) As humans and dogs have similar basic globe and orbit anatomy the STB technique could be extrapolated for canine use. However there are differences encountered when performing this technique in dogs, therefore minor alterations were required to create a practical and effective technique. The developed canine STB technique is described step-by-step in the following chapter.

The sub-Tenon's block technique developed for dogs

A basic set of surgical instrumentation was required, an eyelid speculum, curved mosquito hemostat, 0.5mm rat toothed thumb forceps, and curved Westcott conjunctival scissors (Figure 16). The block technique is described below, and is illustrated by figures 8-16. The local anaesthetic chosen for the STB technique was bupivicaine 0.25% or 0.5% (Marcaine, AstraZeneca, North Ryde, Australia) as determined by the created dosing schedule (Table 5).

Under general anaesthesia the eye was surgically clipped, and prepared with 0.05% chlorhexidine solution, and topical anaesthetic (0.5% proxymetacaine, Alcaine, Alcon, Frenchs forest, Australia) was placed on the dorsolateral bulbar conjunctival surface. An eyelid speculum was placed and mosquito haemostats attached to the perilimbal dorsolateral bulbar conjunctiva to fix the globe in a ventromedial rotated position (figure 8). A small snip incision was made in the dorsolateral bulbar conjunctiva with the scissors, 5mm posterior to the limbus (figure 9-10). A small volume of the local anaesthetic (0.1ml) was infused into Tenon's capsule deep to the conjunctival incision (figure 11). This hydrated the connective tissue and assisted identification of this layer. Tenon's capsule was grasped with forceps and bluntly dissected through with scissors to reach the sclera (figures 12, 17, 18). The scissor tips were then directed posteriorly, staying on the 'line of latitude' between the dorsal rectus and lateral rectus extraocular muscles, immediately exterior to the sclera. This is sub-Tenon's space. Blunt dissection is continued to create a sub-Tenon's tunnel, until the scissor tips are posterior to the globe equator (approximately when the scissor hinge had reached the conjunctival incision) (figures 13). A 19G curved flattened sub-Tenon's cannula (19G 1", Sterimedix, Redditch, UK) attached to a syringe containing the required dose of local anaesthetic was introduced, following the curvature of the globe until the tip was posterior to the globe equator (figures 14-15). The solution was slowly infused into sub-Tenon's space, rotating the cannula tip to

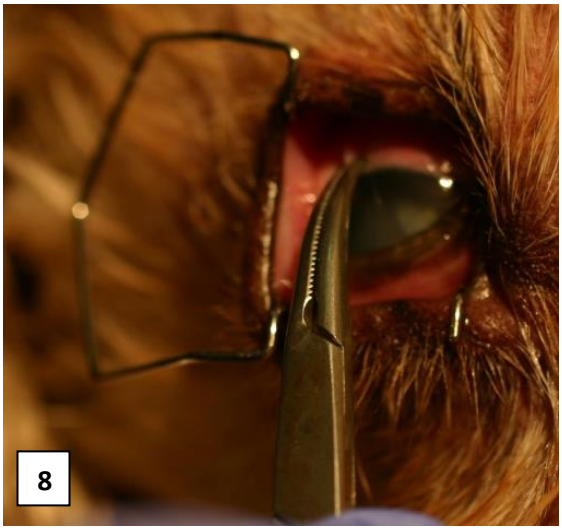
maximise the solution's spread throughout the region. The cannula was then withdrawn and the patient taken to theatre for surgery.

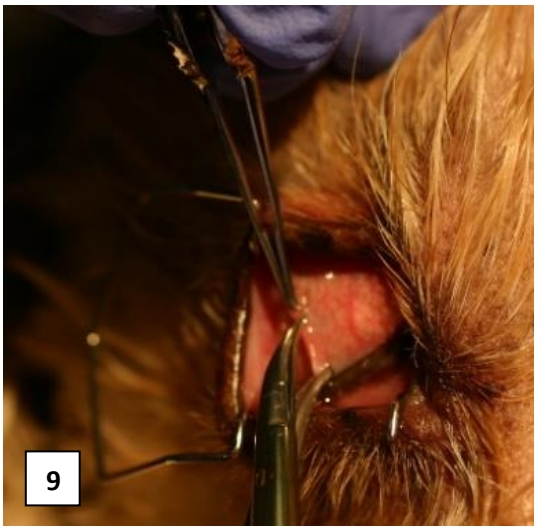
During development of this technique specific approaches were found to greatly increased the rate of successful block placement.

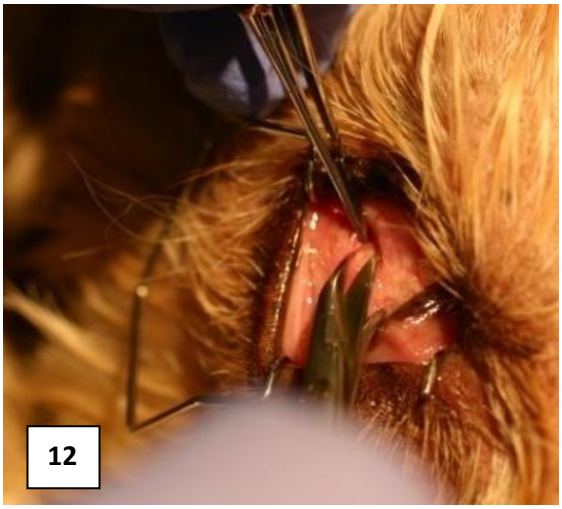
- Hydration of Tenon's capsule at the conjunctival incision facilitated confident dissection down to the sclera. If Tenon's capsule was not entirely dissected through at this stage, sub-Tenon's tunnel creation was difficult and would often lead to intra-Tenon's deposition of bupivicaine, and an ineffective block.
- The blunt dissection during sub-Tenon's tunnel creation was found to be much easier if the scissors were truly in sub-Tenon's space. If blunt dissection is difficult, the scissors may be intra-tenon's and the dissection plane needs to be deeper, immediately adjacent to sclera. Using sharp dissection at this stage should be avoided as it has been associated with globe perforation, and sub-dural infiltration of local anaesthetic.(172)
- Continuing the posterior sub-Tenon's tunnel dissection along the same 'line of latitude' dorsolaterally avoids an oblique cannula placement, and avoids interfering with either the dorsal or lateral rectus extraocular muscles. Initial placement of a haemostat on the perilimbal dorsolateral conjunctiva provides globe fixation for dissection and acts as a marker for the line of dissection.
- Pressing the cannula tip gently into the sclera as it is advanced posteriorly though sub-Tenon's tunnel prevents intra-Tenon's cannula placement. This deflect Tenon's capsule up and away from the cannula tip and avoids the tip becoming encased in Tenon's capsule.
- Marked resistance to flow accompanied with chemosis often indicates that the cannula is intra-Tenon's. The cannula should be withdrawn and the sub-Tenon's tunnel re-established with blunt dissection, or deeper cannula placement.
- Ensuring that the cannula tip is posterior to the globe equator before local anaesthetic infusion begins reduces the amount of fluid which refluxes anteriorly through the conjunctival incision. This also reduces the risk of chemosis.
- Resistance to flow is commonly encountered when the STB infusion is started. The cannula often needs to be withdrawn slightly to allow the solution to start flowing.

- A slow and steady infusion while rotating the cannula tip helps spread the solution throughout the intraconal region. Special effort should be made to rotate the tip ventromedially to ensure good solution contact to the regions away from the site of cannula insertion. This increases the chances of coating all of sub-Tenon's space with local anaesthetic and achieving a more complete block.

Figures 8-16: 8: Eyelid speculum placement and dorsolateral perilimbal clamp placement; 9-10: Conjunctival snip incision 5mm posterior to the limbus, note exposure of the white tenons capsule; 11: hydration of tenons capsule; 12-13: blunt dissection to sub-Tenons space and tunnel creation; 14-15: placement of sub-Tenon's cannula for infusion; 16: Instruments required for a sub-Tenon's block.



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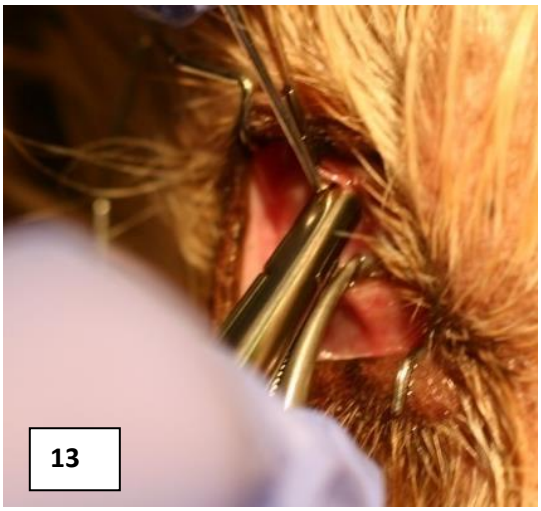
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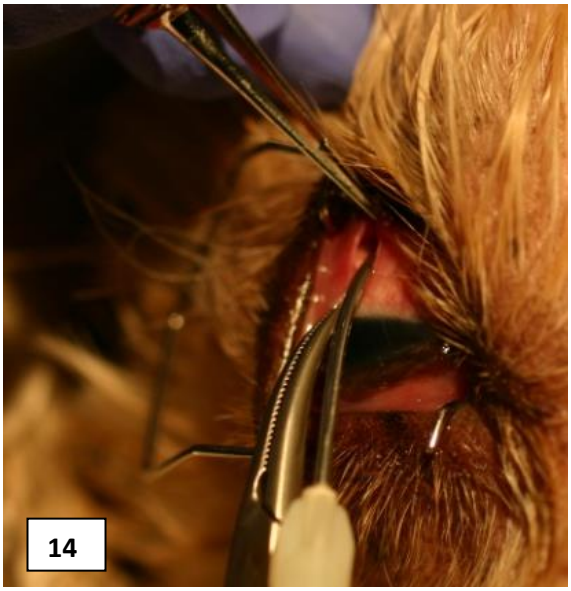
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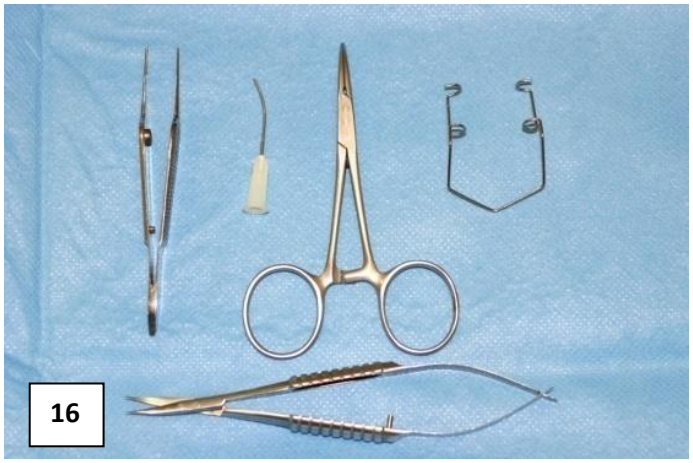
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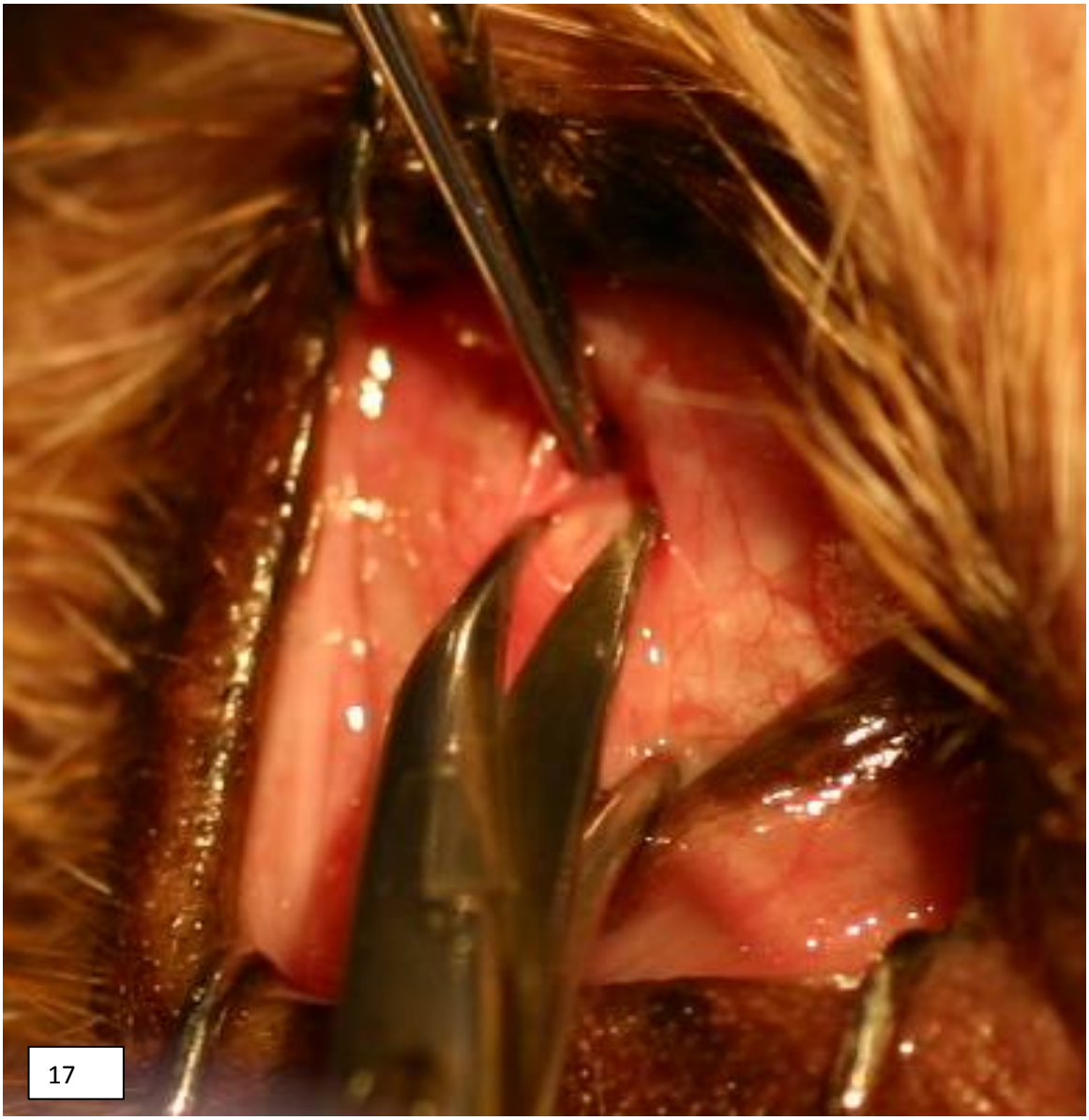
Figures 17 and 18: These enlarged photos show the key stage of dissection through Tenon's capsule to expose sclera. This is the point where dissection to form sub-Tenon's tunnel is started. Figure 17 is a larger image of figure 12 above. Figure 18 has been modified to highlight the various anatomical layers important to sub-Tenon's tunnel creation. The white region is sclera, the yellow region is Tenon's capsule, and the surrounding red region is bulbar conjunctiva. Note that the forceps are grasping Tenon's capsule, not conjunctiva.



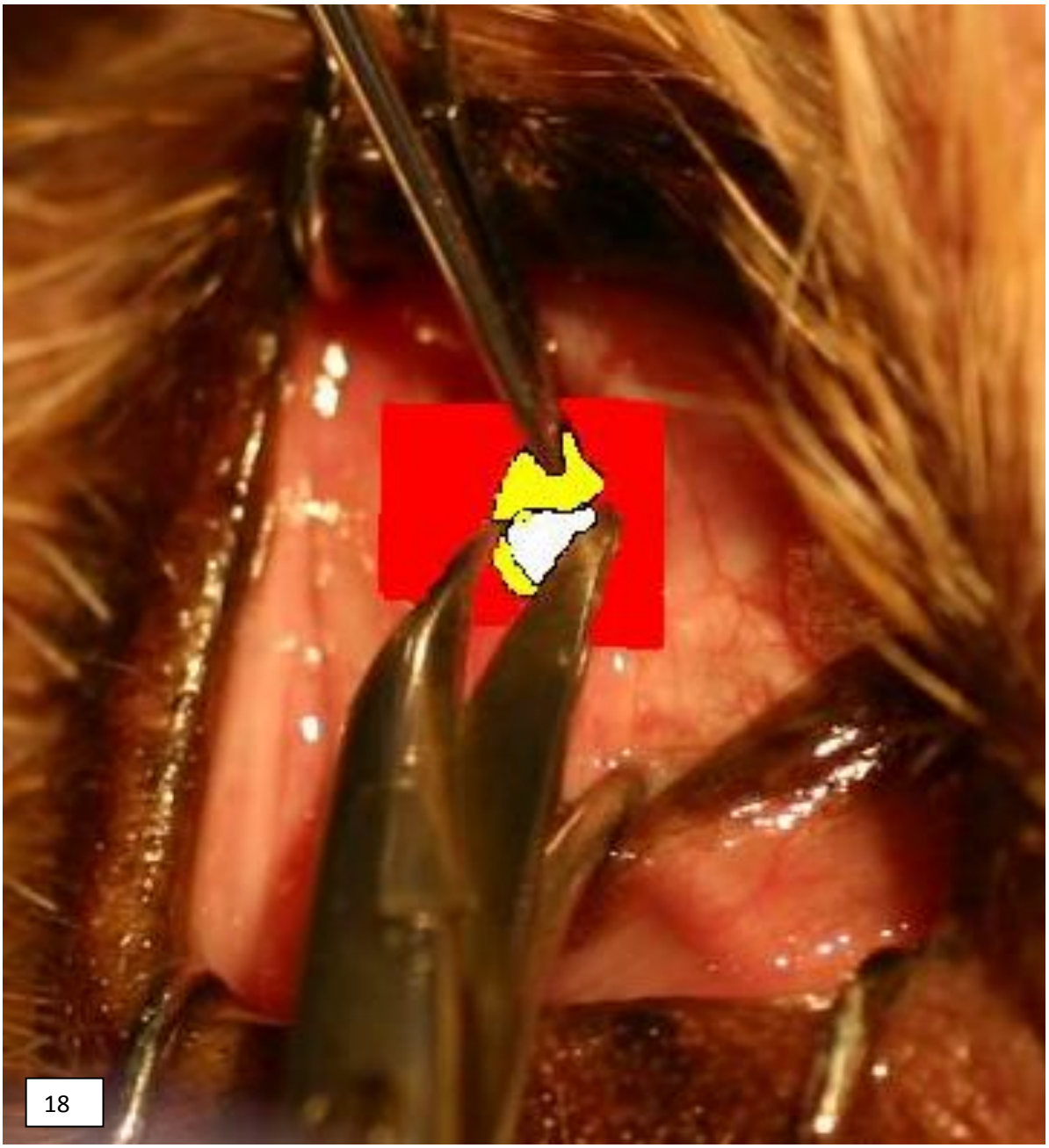

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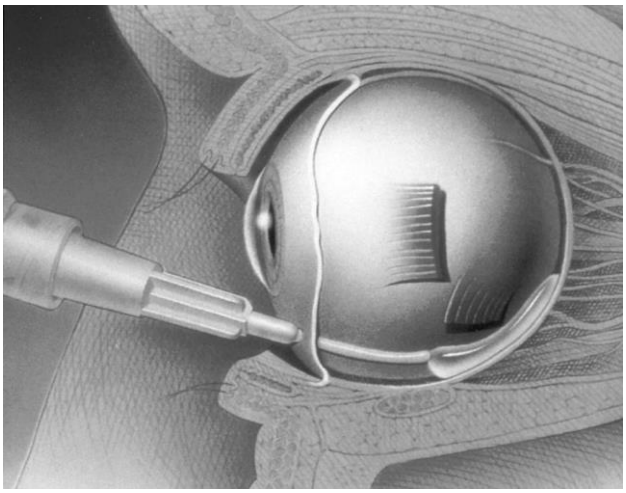
Figure 19. Diagram showing injection of local anaesthetic into the posterior sub-Tenon space in a human eye.(9) Note that this injection is occurring in the ventral region, which is commonplace in human surgery.



Discussion

Orbital regional anaesthesia has been common practice for human cataract surgery for a very long time.(2) Local anaesthetic techniques are growing in popularity, with less procedures being performed under general anaesthesia.(5, 200) In addition to this, there appears to be a shift away from sharp needle techniques, and towards sub-Tenon's anaesthesia.(5) It is likely that these two changes are connected, as sub-Tenon's anaesthesia provides a safe and effective alternative to sharp needle techniques, which may increase ophthalmologists desire to use this technique across a variety of patients.(5, 9, 61)

Regional anaesthesia of the orbit in animals has been previously achieved with retrobulbar injection, peribulbar injection, or a splash block technique. The main application has been as an adjunct analgesic for enucleations, however there are some reports of its usage for intraocular surgery.(30-32, 136, 182, 197, 198) Orbital injection (peribulbar or retrobulbar) techniques have not gained wide application in small animal ophthalmology. This is probably due to the perceived risk of introducing a sharp needle blindly into the orbit damaging the nerves, blood vessels, and globe. Large scale human studies have shown that the actual complication rate associated with orbital injections is very low.(4, 5, 61) Despite this, veterinarians have actively sought out alternative approaches. Veterinarians instead rely on post-operative splash blocks or systemic analgesics for post-operative analgesia, or systemic

neuromuscular blockade for extraocular muscle paralysis.(141, 186) Systemic neuromuscular blockade is not without its own risks and complications, as respiration need to be closely monitored and often supplemented with mechanical ventilation to prevent respiratory acidosis, hypercapnia and hypoxia.(185, 188)

Veterinary research has recently been published that investigates orbital anesthetic techniques that are different to the traditional retrobulbar injection. A peribulbar injection technique has been developed in cats that had a higher rate of intraconal solution deposition when compared to a retrobulbar injection.(7, 198). This peribulbar injection technique appears to be a viable alternative to retrobulbar injection in cats and this newer technique may avoid the complication of brain stem anaesthesia(196) Two separate articles were recently published showing the effectiveness of a splash block local anaesthetic technique for analgesia after enucleation in dogs.(31, 32) These studies have shown that a post-enucleation splash block provided equivalent analgesia when compared to dogs that received a pre-operative retrobulbar injection. Sub-Tenon's anaesthesia has been tested in experimental dogs and appears to be a viable alternative to systemic neuromuscular blockade for mydriasis and extraocular muscle akinesia.(189, 199) Unfortunately the sub-Tenon's block technique was not described in these publications, therefore a technique needed development to further investigate sub-Tenon's anaesthesia.

The basic human STB technique required some alteration to create an effective canine technique. This was due to the more highly developed Tenon’s capsule present in dogs, and the globe rotation which occurred under general anaesthesia. STB placement in people is generally performed by snipping the conjunctiva and pushing the sub-Tenon’s cannula into the sub-Tenon’s space. Cataract surgery in humans is most commonly performed on aged people with weaker collagen structure, therefore this approach is effective (201, 202). When cataract surgery is performed in children, blunt dissection and sub-Tenon’s tunnel creation is often required due to the relatively thicker Tenon’s capsule layer.(Personal communication: Dr Helen Long) As dogs have a comparatively thicker Tenon's capsule, cannula placement into sub-Tenon’s space was impossible without blunt dissection and sub-Tenon’s tunnel creation. Once the sub-Tenon's tunnel is established, infusion of STB was simply performed. In humans the ventromedial region is the preferred site for STB placement as any subconjunctival haemorrhage or chemosis as a result of the STB doesn't interfere with cataract surgery. The

patient is asked to 'look up and out' to expose the ventromedial region and the STB is placed. In anaethetised dogs, the ventromedial region is very difficult to access due to ventromedial rotation of the globe, and the presence of the nictitating membrane (third eyelid). Block placement in this region in dogs would be very difficult so a different location was used. Due to the ventromedial globe rotation, the exposed dorsolateral region was the obvious choice. Chemosis in this region could affect the cataract surgery incision due to its close proximity, however it is unlikely that surgery would be detrimentally affected.(9) Testing of effective extraocular muscle akinesia in dogs is not as straight forward as in human patients, which are simply asked if they can move their eye after a STB. Other markers of akinesia must be used in the veterinary field. These include globe centralization and pupillary dilation. Globe centralization indicates extraocular muscle paralysis, as the globe rests in a central location when there is no extraocular muscle tone.(82) Whilst pupillary dilation is not specifically an indicator of extraocular muscle paralysis, it can be a sign of orbital anaesthesia. Pupil dilation occurs with blockade of the ciliary nerves as they pass through the intraconal region, resulting in paralysis of the pupil sphincter muscle.(90) Mydriasis indicates presence of the local anaesthetic in the intraconal region and therefore in an affective location to cause extraocular muscle paralysis.

As with any new procedure, there is a learning curve for its effective application. One publication discusses this for human STB, suggesting that the learning curve to achieving a successful block is around 60 cases.(203) While specific attention was not paid to the length of the learning curve for this canine technique, the author estimates that the learning curve from a novice to routinely and confidently placing successful STB anaesthesia was around 10-20 cases. It is possible that future veterinarian learning curves may be shorter if they follow the technique described in this publication. It is recommended to begin learning the technique on enucleation or ISP cases to become familiar with the approach before using it for cataract surgery. If STB placement is unsuccessful in enucleation and ISP cases a splash block technique can be used to provide appropriate post-operative analgesia.(31, 32) If STB anaesthesia was unsuccessful in a cataract surgery case systemic NMB could be used to provide the required extraocular muscular paralysis. As there are legitimate ‘back up’ options for an ineffective STB veterinarians can confidently trial this new technique.

This STB technique used a single local anaesthetic agent, Bupivicaine, at a concentration of either 0.25% or 0.5% and a volume as per the created dosing schedule (Table 5). Many previous studies have tested a variety of local anaesthetic compounds for orbital regional anaesthesia, either as sole agents or as a mixture.(9, 30, 87, 132, 198, 199, 204, 205) Bupivicaine was chosen largely for its prolonged length of activity compared to other local anaesthetics. A long length of activity is required to maintain effect throughout the length of surgery and to maximise the post-operative analgesia. The main disadvantage of bupivicaine is its reported slow onset of action. A mixture of bupivicaine, lidocaine and hyaluronidase is often used for human cataract surgery to minimise the length of time from STB placement to achieving anaesthesia for cataract surgery.(9, 150, 175) As most of these procedures in humans are done without general anaesthesia, the 'time to onset of effect' of the block is the main source of delay between cases. All canine cataract surgeries are performed under general anaesthesia to ensure appropriate immobilisation for surgery. The additional time required for induction and maintenance of general anaesthesia, combined with moving and positioning the patient, surgical scrubbing and equipment setup means that the 'time to onset of effect' of local anaesthesia is not a rate limiting step for canine cataract surgery. Anecdotally the author noted extraocular muscle paralysis was achieved within 30 seconds of block placement as many eyes were rotating centrally before the bupivicaine had been completely infused. It therefore appears that the onset of action of bupivicaine for STB is generally rapid and any difference with a more 'rapidly acting' local anaesthetic drug is likely to be negligible.

Sub-Tenon's anaesthesia infuses local anaesthetic with the intraconal region, therefore periorbital structures are often unaffected by this block. For human cataract surgery, eyelid akinesia is important to prevent blepharospasm and squinting. This is usually achieved with a relatively high volume STB (5ml), in combination with hyaluronidase.(Personal communication: Dr Helen Long) (9, 175) This volume combined with an enzyme that encourages diffusion results in local anaesthetic tracking up the facial planes from the orbit into the eyelid.(90, 104, 121, 170, 206) If this is ineffective a facial nerve block is then used.(3, 9, 89) Eyelid akinesia is less important in canine ophthalmic surgery as the procedures are performed under general anaesthesia rendering the eyelid function greatly reduced or abolished. This lack of effect in the eyelids however may be relevant in enucleation cases where the eyelid skin is excised. This could result in a lack of anaesthesia in the eyelid tissue and increased post-operative discomfort. This effect is theoretical, however concurrent use of subcutaneous local anaesthetic with retrobulbar anaesthesia has been advocated.(181)

Conclusion

The established human STB technique provided an excellent basis to develop an effective STB technique for dogs. Sub-Tenon's anaesthesia has great potential to provide anaesthesia and analgesia for canine ophthalmic surgery. The next step in to trial this new STB technique across a population of dogs undergoing ophthalmic surgery to assess its true application in clinical canine ophthalmology.

CHAPTER 3

Efficacy of sub-Tenon's anaesthesia in canine ophthalmic surgery

Introduction

Sub-Tenon's anaesthesia has a high safety and efficacy in human ophthalmic surgery, and has resulted in a shift away from sharp needle retrobulbar and peribulbar injections. This technique has many possible applications in canine ophthalmic surgery, with the potential to alter standard practice for post-operative analgesia, and to supersede systemic neuromuscular blockade for cataract surgery. The purpose of this study was to test a sub-Tenon's block (STB) technique in dogs by assessing three key factors; the effect on analgesia, the suitability of STB as an alternative to systemic neuromuscular blockade for cataract surgery, and identification of any complications associated with STB. By assessing STB across a variety of canine ophthalmic surgeries an indication of the potential practical applications of this new technique can be reported.

Materials and methods

Study type

A prospective, randomised, blinded, controlled clinical study was performed. Approval was provided by the Massey University Ethics Committee and the clinical study was carried out accordingly. Client informed consent was attained for each case admitted into the study.

Study population

The population consisted of client owned dogs that presented to the Veterinary Ophthalmic Referrals clinic (204 ANZAC highway, Plympton, Adelaide, South Australia, Australia) for ophthalmic surgery between dates of 24/11/2014 - 12/8/2015. These cases required surgery due to either: corneal surface disease, cataract, glaucoma, uveitis, keratoconjunctivitis sicca, or intraocular neoplasia. The surgeries included in this study were of four types: Superficial keratectomy with nictitans flap (SK), , enucleation with intraorbital implant, evisceration with intraocular implant (ISP) and phacoemulsification for cataract extraction. These surgical techniques are well described in standard veterinary ophthalmic textbooks.(82, 141) The surgeries of keratectomy with nictitans flap, enucleation with intraorbital implant and evisceration with intraocular implant were combined for analysis of certain variables as was appropriate and are referred to as the 'non-cataract surgeries'. This classification assists distinction between results from these procedures and the bilateral cataract surgeries and simplifies the reporting of results. Some surgeries were excluded due to possible adverse effects from the sub-Tenon's block (STB) (Appendix A). Non-cataract surgical cases were

randomly assigned to the treatment or control group according to a pre-designated random allocation list. Bilateral cataract surgery cases were managed as matched pairs with the eye receiving STB designated by a coin toss. Surgery on the contralateral eye was performed under a low-dose systemic neuromuscular blockade (NMB), considered standard practice for this surgery.(141, 185, 186)

General anesthetic technique

The anesthetic technique was standardised across all groups to minimise variation. Dogs were pre-medicated with subcutaneous acepromazine (0.01-0.025mg/kg, A.C.P 2, Delvet, Seven Hills, Australia) and buprenorphine (0.01mg/kg, Temgesic, Reckitt Benckieser, West Ryde, Australia). The acepromazine dose was varied for bodyweight ranges as anecdotally larger dogs are more sensitive to its sedative effects at a given mg/kg dose than small dogs (Appendix B). The dogs were induced with intravenous propofol dosed to effect (2.5-4mg/kg, Fresofol 1%, Fresenius Kabi, Pymble, Australia) to allow endotracheal intubation. Anaesthesia was maintained with inhaled isoflurane (Dosed to effect, Isoflurane, Ceva, Glenorie, Australia) in 100% oxygen until the completion of surgery. Under anaesthesia the eyelids were clipped, and the globe and adnexal tissues surgically prepared with 0.05% chlorhexidine solution (Chlorhex-C, Jurox, Rutherford, Australia). The cases in the treatment group received STB with either 0.25% or 0.5% Bupivicaine (Marcaine, AstraZeneca, North Ryde, Australia) at a pre-determined dose and volume according to the dog's weight (Table 5). All STB were placed by the author. Surgeries were performed by one of two surgeons (Kellam Bayley, R. Tony Read). Any alterations to a standard surgical technique, intraoperative complications or difficulties were recorded for all groups. At the time of extubation, animals received subcutaneous carprofen (2mg/kg, Rimadyl, Pfizer, West Ryde, Australia) and intravenous acepromazine (0.01mg/kg). Exclusion criteria for post-operative acepromazine was outlined before data collection began (Appendix C). All animals received supportive intravenous isotonic crystalloid fluids at 10ml/kg/hr during anaesthesia, and maintenance rates for a few hours after extubation. Anaesthetic parameters were recorded at 5 minute intervals throughout surgery, including: heart rate, respiratory rate, systolic and mean blood pressure (petMAP graphic, Ramsey medical Inc., Tampa, USA), isoflurane vaporiser setting (Isotec-5, Datex-Ohmeda, Steeton, England), pulse oximetry and capnography (CO_2SMO monitor, Respironics, California, USA).

Table 5: Dosing schedule for the sub-Tenon's block

Weight range	Volume and bupivicaine concentration
<5kg	2ml 0.25% bupivicaine
5-9.9kg	3ml 0.25% bupivicaine
10kg +	3ml 0.5% bupivicaine

Intraocular pressure measurement

After inducing general anaesthesia and intubation, the dog was positioned in sternal recumbency and the chin was supported with a bean bag to elevate the head slightly for tonometry. Care was taken to avoid tension around the neck which can artificially raise intraocular pressure (IOP). IOP was measured for all surgical cases receiving STB with a rebound tonometer (Tonovet Tonometer, Tiolat Oy, Helsinki, Finland) immediately before and after STB placement. For bilateral phacoemulsification cataract surgery cases IOP measurements were taken in both the STB and untreated eye before and after STB placement.

Assessment parameters for bilateral cataract surgeries

Specific parameters were directly observed and subjectively assessed before and during surgery to estimate the impact of the STB compared to control eyes receiving NMB. These parameters were assessed by the senior specialist ophthalmologist and included: globe rotation, anterior-posterior globe position within the orbit, pupil dilation, anterior chamber depth, and vitreal expansion. Globe rotation was assessed as either central or not central depending on if the visual axis was in a neutral, forward projecting position, or not. Anterior-posterior globe position within the orbit was assessed according to the globes' position in relation to the eyelids and orbital rim. This was judged as either exophthalmic, neutral, or enophthalmic as compared to the control eye. Dogs of different breeds have a large variation in orbit depth.(82) Therefore any comparison of anterior-posterior globe position within the orbit under general anaesthesia between breeds would be fraught with difficulty, hence a matched pair design was used. Pupil dilation was subjectively assessed and recorded as either dilated or not dilated. Vitreal expansion and anterior chamber depth were assessed according to the tendency of the iris and posterior lens capsule to protrude anteriorly during surgery in comparison to the control eye. For bilateral cataract surgeries the eye that received the pre-operative STB was always operated on first. This was to avoid any confounding effects due to

residual NMB used for surgery on the control eye, however this order prevented blinding the surgeon to the treatment group which the eye of interest belonged to. For intraoperative assessment of NMB treated eyes, the globe position, rotation and pupil dilation assessments were performed before administering NMB to allow comparison of the effects of STB to an 'untreated' eye. Anterior chamber depth and vitreal expansion could only be assessed after entry into the anterior chamber and by necessity had to be assessed after administration of the NMB at the time of corneal incision. Therefore the effect of STB was directly compared to the effect of NMB for these two parameters. If pupillary dilation was insufficient to perform cataract surgery, 1:10000 diluted intracameral adrenaline (Adrenaline-Link. Adrenaline 1mg/ml, 1 in 1000, LinkPharma, Warriewood, NSW, Australia) was used to enhance dilation. Both STB and NMB eyes had received pre-operative tropicamide, so any pupillary dilation cannot be solely attributed to the type of block.

Variations between control groups for different surgeries

The various surgical groups received different medications as appropriate for the procedure (Table 6). The keratectomy control group received no additional local anaesthesia. The enucleation and ISP control groups received an intraoperative splash block with 0.5% bupivicaine upon globe, or intraocular content removal. The phacoemulsification cataract surgery eyes were treated for an hour pre-operatively with the topical mydriatic tropicamide (Minims Tropicamide 1%, Chauvin, Macquarie Park, NSW, Australia) and the non-steroidal anti-inflammatory agent ketorolac (Acular, Ketorolac trometamol 5mg/ml, Allergan, Gordon NSW, Australia). Cataract surgery control eyes received low-dose systemic neuromuscular blockade (NMB) using intravenous pancuronium (0.01mg/kg Pancuronium bromide BP, Astrazeneca, North Ryde, Australia) intra-operatively after stay suture placement for extraocular muscle paresis and reduction of vitreal expansion.

Table 6: Outline of additional medications given to the surgery groups

Surgical procedure	Topical medications	Systemic medications	Regional local anaesthesia
Keratectomy	n/a	Carprofen, Acepromazine	n/a
Enucleation	n/a	Carprofen, Acepromazine	Bupivicaine splash block in control group only
Intrascleral prosthesis	n/a	Carprofen, Acepromazine	Bupivicaine splash block in control group only
Cataract extraction	Tropicamide, ketorolac	Carprofen, Acepromazine. Pancuronium in control eye only	n/a

Post-operative pain scoring

A subjective assessment of the pain experienced by each case was made using a pain scoring system from previous veterinary ophthalmology post-operative pain scoring studies, with minimal modification (Appendix D). (30-32, 78) Using this established pain scoring system allowed some comparison of data in this study with the previously published work. The pain scoring was performed by one of four trained veterinary technicians who were blinded to the treatment group. The specific technician performing the pain score assessment varied between individual cases, however the same technician performed pain scores assessments on individual cases throughout the time in hospital. Dogs were assessed before premedication to provide a baseline, then at extubation (time 0) and at times 15, 30, 45, 60, 90, 120, 240, 300 minutes after extubation. (Appendix E). The total time period of individual post-operative pain score assessments varied as all cases were managed as day procedures with different surgery times and discharge times. Rescue analgesia was provided if the pain score in a single category was 3 or higher, or if the total score was 9 or higher. Following rescue analgesia, pain score recording was discontinued for that case. Rescue analgesia consisted of intravenous buprenorphine (0.02mg/kg). If buprenorphine alone was inadequate to settle the animal,

additional sedation was achieved with either intravenous medetomidine (0.005mg/kg, Domitor, pfizer, West Ryde, Australia), or intravenous acepromazine (0.01mg/kg).

Post-operative follow-up

Post-operative complications and outcomes were recorded in all cases for 14 days after surgery.

Statistical testing

An a priori power calculation was performed to estimate the case numbers required for this study. This data set contains many different types of measurements and assessments, across different surgery groups, and different treatment groups. Statistical software was used to analyze the data (R v 3.1.0; R development core team, 2012; R foundation for statistical computing, Vienna, Austria). Significance was inferred at $p \leq 0.05$. One sample t tests were used to assess for changes between intraocular pressure before and after STB. This was the appropriate technique to assess this normally distributed numerical data. Two tailed Wilcoxon signed-rank test was used to test for a difference in the mean general anaesthetic parameters in the cataract surgery group. This allowed testing of the paired non-parametric data between the STB and control NMB treated eyes. Two tailed Wilcoxon rank sum tests were performed on the non-parametric data from the enucleation group general anaesthetic parameters and the post-operative pain score data for the enucleation and keratectomy surgery groups. Fishers exact test for association was used to assess the rate of central globe position in the non-cataract surgical cases, the rate of pupil dilation in the non-cataract surgery cases, and to assess for the risk of post-operative complications between treatment and control groups. Probability graphs were produced to depict the outcomes from this testing. McNemars chi squared test with continuity correction was used to test the rate of central globe position in the cataract surgery cases, as these were matched pairs with nominal data. An exact binomial test was used for the subjectively assessed parameters in the cataract surgery group. These tested whether the anterior chamber was shallower in the treatment group than the control group, and if the vitreal expansion was greater in the treatment group than the control group. Making this data suitable for binomial assessment simplified the testing, and increased the opportunity to detect a clinically significant difference between the treatment groups.

Results

Study population

A total of 54 dogs were enrolled in this study, the distribution of cases is summarised in Table 7. The mean age of the dogs was 8.72 years (σ = 3.55, range=0.9–17) (Appendix F). The mean bodyweight was 17.7kg (σ =13.4kg, range = 4.6-65kg) (Appendix G and H). The sex distribution was quite even through this study, with 22 neutered females, 2 entire females, 23 neutered males, and 7 entire males. There were 30 breeds represented in the study population, with the most common type being Maltese cross (n=11) followed by Boxers (n=5) while most remaining breeds were represented by a single dog (23 single dog breeds) (Appendix I)

Table 7: Distribution of the study population across the different surgeries and treatment groups

Surgery group	**Study group**	
	Control	**Sub-Tenon's block**
Superficial keratectomy and third eyelid flap	11	12
Enucleation	7	7
Intrascleral prosthesis	3	2
Bilateral cataract surgery	12	

Assessment of analgesia

The intraoperative anaesthetic parameters were assessed in the enucleation and bilateral cataract surgery groups. There was too little data for analysis from the keratectomy group due to a short surgical length (10-15 minutes) and too few cases to assess in the ISP group. The findings are presented in Tables 8 and 9.

Table 8: Wilcoxon signed rank test results on parameter means for the bilateral cataract surgery group. Both the p value and w value are presented due to the relatively low population size (n=12). With a significance level at p≤0.05, the critical W value is <13. The p value was calculated from wilcoxon z value. (Iso %: isoflurane vapouriser setting, HR: heart rate (beats/min), BPsys: Systolic blood pressure (mmHg), BPmean: Mean blood pressure (mmHg), RR: respiritory rate (breaths/min)

GA parameter	Mean value		Standard deviation		Median		Wilcox. p value	Wilcox. W value
	Control	STB	Control	STB	Control	STB		
Iso %	2.3	2.32	0.48	0.4	2.2	2.4	0.968	38.5
HR	101.97	98.53	21.09	19.67	102	98	0.523	31
BPsys	119.24	112.17	13.97	15.22	118.5	111	0.019	9
BPmean	76.94	72.78	8.91	8.78	75	73	0.019	9
RR	17.45	18.91	10.45	10.69	15.5	15	0.529	31

Table 9: Wilcoxon signed rank test results for these parameters in the control and STB cases in the enucleation surgery group. The p value was calculated from wilcoxon z value. (Iso %: isoflurane vapouriser setting, HR: heart rate (beats/min), BPsys: Systolic blood pressure (mmHg), BPmean: Mean blood pressure (mmHg), RR: respiritory rate (breaths/min)

GA parameter	Mean value		Standard deviation		Median		Wilcox. p value
	Control	STB	Control	STB	Control	STB	
Iso %	2.44	2.26	0.58	0.49	2.5	2	0.069
HR	95.51	86.19	20.02	13.92	103	85	0.019
BPsys	120.58	113.53	23.67	9.9	112	112	0.335
BPmean	78.25	76.76	15.07	10.37	74	77	0.756
RR	19.43	19.45	18.25	26.27	16	10	0.083

In the bilateral cataract surgery group there was a statistically significant difference between the STB and control eyes for the systolic and mean blood pressure parameters. Similarly there is a statistically significant difference in the heart rate between the control and STB cases in the enucleation group. Changes of these levels did not significantly impact the study group mean or standard deviation to a level which could be detrimental to the patient. Study groups with larger numbers would be required to investigate if these changes are consistent in future studies, however in this study changes of this magnitude in these parameters are highly unlikely to have clinical significance.

The end tidal carbon dioxide ($ETCO_2$) levels were measured in all cases. The levels in the non-cataract surgery groups showed significant overlap of values throughout the anaesthetic (Figure 20). The levels in the cataract surgery group also showed some overlap in values. Data from one of these cases was removed from analysis due to erroneous recording (n=11). The cataract surgery group results were tested for a difference between the STB and control NMB treated eyes. The mean difference in $ETCO_2$ was +2.79mmHg CO_2 (σ=3.65, range=-2 - +9.33). This difference did not quite reach significance (p=0.05, w=11 (for an n=11 sample, the critical value for w is < 10)). The results were depicted differently than for the non-cataract surgery cases to illustrate the changes in values through time, as the control and STB values for the bilateral surgery cases were gathered throughout the same anaesthetic period for each case (Figure 21).

Figure 20: $ETCO_2$ levels for non-cataract surgery cases from the STB and control groups

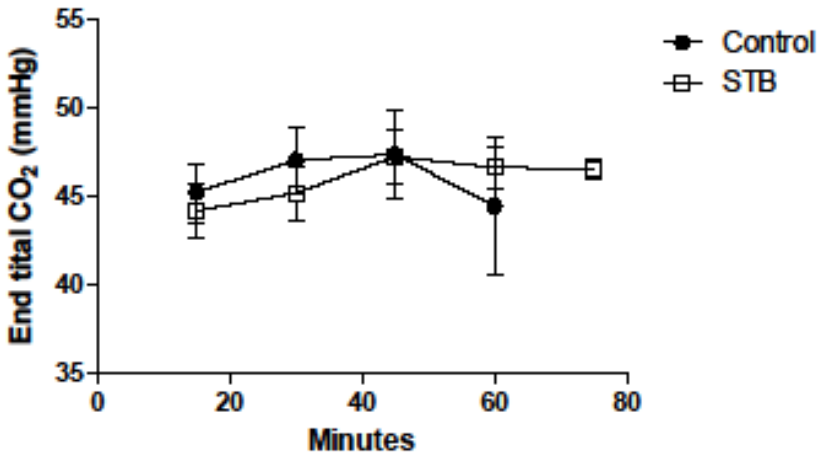
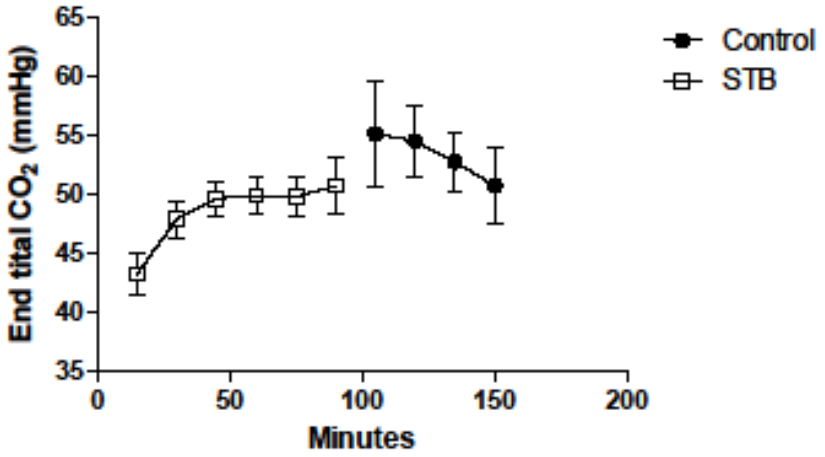


Figure 21: $ETCO_2$ levels for the bilateral cataract surgery cases for both STB and NMB (control) treated eyes



All cases in this study underwent pain score assessment before and after surgery. The length of post-operative assessment was variable due to dogs being removed due to aggression (n=1), rescue analgesia requirement (n=3), and varying lengths of hospital stays after surgery. Post-operative acepromazine was used in 45 cases (83%) as previously described. The post-operative pain scores were assessed with a wilcoxon rank sum test to test for a difference in between the STB and control groups in the enucleation and keratectomy groups. Only descriptive statistical data is presented for the ISP group due to a small number of cases in this surgical group.

Table 10: Post-operative pain scores for cases following enucleation. # denotes cases removed for elevated pain score. Significance was inferred at p ≤0.05. * indicates where there is too little data for analysis and only the descriptive statistics are reported.

Time (Min)	Mean pain score		Standard deviation		Number (n)		Wilcox. p value
	Control	STB	Control	STB	Control	STB	
-77	0.8	1.1	0.53	0.59	7	7	0.124
0	0.66	0.23	1.28	0.6	7#	7	0.277
15	0.53	0.51	0.68	0.78	6	7	0.698
30	0.73	0.63	0.64	0.6	6	7	0.567
45	1	0.63	0.53	0.6	6	7	0.026
60	0.9	0.71	0.71	0.52	6#	7	0.41
90	0.75	0.83	0.64	0.46	4	6	0.586
120	1	0.76	0.65	0.44	3	5	0.315
150	1	0.7	0.67	0.47	2	4	*
180	1	0.8	0.67	0.45	2	1	*

Table 11: Post-operative pain scores for cases following keratectomy and third eyelid flap. # denotes cases removed for elevated pain score. Significance was inferred at p ≤0.05. * indicates where there is too little data for analysis and the values are just reported.

Time (Min)	Mean pain score		Standard deviation		Number (n)		Wilcox. p value
	Control	STB	Control	STB	Control	STB	
-77	0.78	0.86	0.67	0.72	11	12	0.618
0	0.35	0.39	0.62	0.66	11	12	0.813
15	0.62	0.61	0.63	0.55	11	12	0.929
30	0.73	0.65	0.65	0.59	11	12	0.593
45	0.76	0.56	0.66	0.58	11	12	0.139
60	0.8	0.56	0.73	0.53	11#	11	0.104
90	0.73	0.55	0.58	0.53	10	10	0.136
120	0.73	0.59	0.61	0.6	8	9	0.307
150	0.78	0.6	0.64	0.63	6	7	0.245
180	0.78	0.6	0.64	0.72	6	5	0.257
240	0.75	0.67	0.62	0.56	2	4	0.75
300	0.67		.052		1	0	*

Table 12: Post-operative pain score data for cases following Intrascleral prosthesis.

Time (Min)	Mean pain score		Standard deviation		Minimum		Maximum		Number (n)	
	Control	STB	Control	STB	Control	STB	Control	STB	Control	STB
-77	0.5	0.67	0.62	0.49	0	0	2	1	3	2
0	0	0.43	0	0.49	0	0	0	1	3	2
15	0.39	0.58	0.7	0.51	0	0	2	1	3	2
30	0.39	0.67	0.61	0.49	0	0	2	1	3	2
45	0.56	0.67	0.62	0.49	0	0	2	1	3	2
60	0.33	0.67	0.49	0.49	0	0	1	1	2	2
90	0.58	0.67	0.67	0.49	0	0	2	1	2	2
120	0.67	0.67	0.81	0.49	0	0	2	1	1	2
150		0.67		0.49		0		1	0	2

There was very little difference found in the post-operative pain scores of the non-cataract surgery groups. The pain scores in the enucleation control group were significantly higher than the STB group 45 minutes after extubation, however this pattern was not continued throughout the pain score assessment period. There was no significant differences found in the keratectomy surgery group, and the descriptive statistical data for the ISP surgery does not suggest any obvious difference between the STB and control groups.

In the cataract surgery group, post-operative pain score analysis was not performed as this matched pairs group served as both STB and control. Therefore any trend could not be specifically attributed to either therapy. The pain scores in this group were all low, with no cases requiring rescue analgesia (Table 13). One case was removed from assessment 30 minutes after surgery due to aggression. This dogs' previous pain scores were all low and he had a history of becoming aggressive upon hospitalisation, therefore it was interpreted as behavioural rather than a pain issue.

Table 13: Mean total pain score, standard deviation, range and number for the bilateral cataract surgery group at each time point that pain scoring was performed. α denotes a case removed from pain score assessment due to aggression.

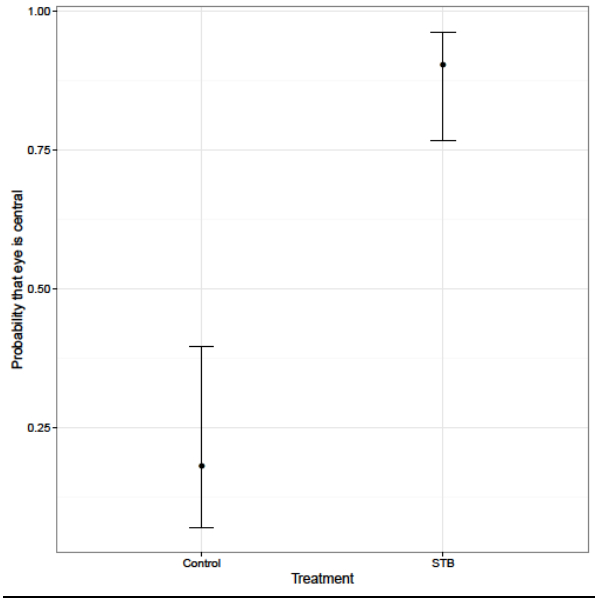
Time (min)	Mean pain score	Standard deviation	Number
-77	0.68	0.33	12
0	0.14	0.21	12
15	0.21	0.18	12
30	0.4	0.18	12α
45	0.55	0.21	11
60	0.55	0.17	11
90	0.55	0.24	11
120	0.56	0.23	11
150	0.57	0.23	7
180	0.5	0.21	6
240	0.5	0.17	3

Three patients (5.6%) in this study required rescue analgesia due to elevated pain score. All of the cases requiring rescue analgesia were from the control group in this study. The cases were as follows: Staffordshire Bull Terrier from the SK control group, Maltese cross and a Tibetan spaniel from the enucleation splash block group. The high pain score and administration of the rescue analgesia occurred at 0 (n=1) and 60 (n=2) minutes after extubation (mean=40 minutes). This time to failure of analgesia is similar to previous canine ocular post-operative pain score studies.(30, 32)

Assessment of regional orbital anaesthesia

Globe rotation was recorded for all cases as either central or non-central. STB treatment was significantly more likely to result in a central globe position in all surgical groups (cataract surgery group p=0.0044, non-cataract surgery groups $p=1.44e^{-8}$). The probability of a central globe from either the control or STB treatment groups is depicted in the graph below (Figure 22).

Figure 22: Probability of a central globe position in the treatment and control groups.



It is worth noting that none of the dogs that received STB lost the palpebral reflex in the post-operative period (26 cases with the enucleations excluded, as a palpebral reflex cannot be assessed in this group). Two small dogs weighing 7.2 and 9.4kg showed a transient upper eyelid ptosis, which self-resolved at 90 and 240 minutes after extubation.

Pupillary dilation (mydriasis) was recorded for all cases as either dilated or non-dilated. In the non-cataract surgery group, cases were excluded from testing if there were pre-existing ocular changes that affected pupil mobility. These changes included glaucoma, iris neoplasia, uveitis and posterior synechia, which resulted in 17 cases being excluded from testing. STB treatment was significantly more likely to result in a dilated pupil in the non-cataract surgery group ($p=2.36e^{-6}$) (Figures 23 and 24). All of the bilateral cataract surgery cases received pre-operative mydriatics and had dilated pupils at the start of surgery, therefore these cases were not assessed for a difference between the STB treated eye and the control eye.

Figure 23: The proportion of eyes with either dilated or constricted pupils in the non-cataract surgery groups

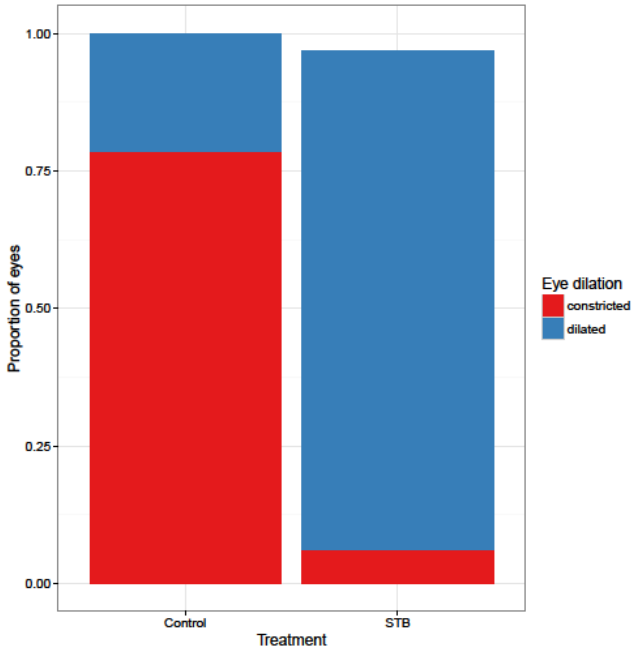
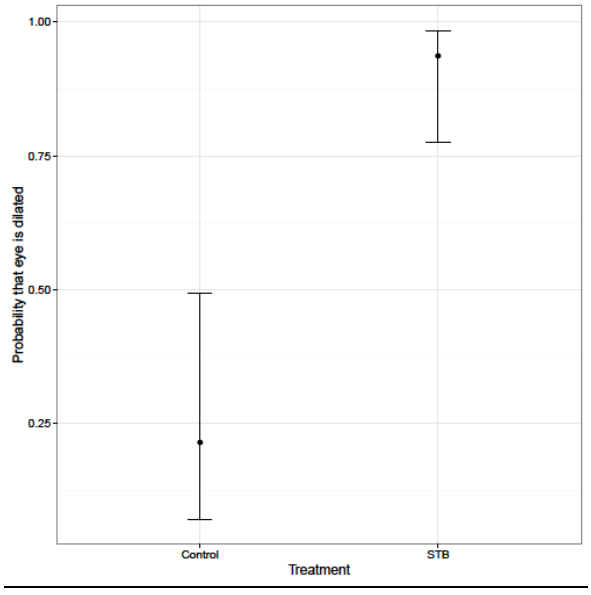


Figure 24: Probability of a dilated pupil in the non-cataract surgery groups



The position of the globe was assessed in bilateral cataract surgery cases. All of the STB treated eyes (12 eyes) were displaced anteriorly when compared to the control eye. Upon surgery completion, this effect was judged to be beneficial, detrimental, or insignificant to the performance of cataract surgery. This effect was beneficial in 6 cases (50%), detrimental in 1

case (8%), and non-significant in 5 cases (42%). The cases which benefited had improved globe exposure, resulting in simpler surgical instrumentation manipulation within the eye. The one case that was affected detrimentally developed significant vitreal expansion, which was theorized to be due to anterior globe movement and compression against the palpebral fissure.

Complications

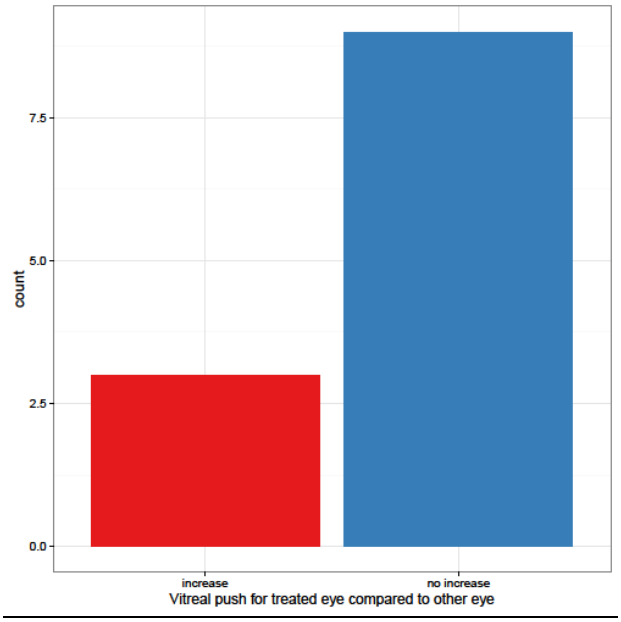
Complications were assessed at three time points; immediately after STB administration, intraoperatively, post-operatively.

After STB administration failure of globe centralisation and pupil dilation occurred in two cases out of 33; one Boxer, and one Great Dane. These were recorded as a failure of technique due to a lack of akinesia after STB placement. This presumably occurred due to the local anaesthetic not being delivered into the intraconal region. Two cases out of 33 had episcleral haemorrhage while the sub-Tenon's tunnel was being created. The volume of haemorrhage was estimated to be 1ml, and 0.2ml. The bleeding was self-limiting and required no intervention to resolve. Both of these cases were having enucleation surgery, one case had glaucoma, and the other had phacoclastic uveitis. Intraocular pressure was measured in all non-cataract surgery cases receiving STB, and in all bilateral cataract surgery eyes as IOP elevation was significant potential complication after STB. In the non-cataract surgery group , there was no significant difference in the IOP before and after STB administration. The 95% confidence interval of IOP change was -1.15mmHg to 1.01mmHg (p=0.89). In the bilateral cataract surgery group the IOP was assessed for change in the STB eye, and compared to the change in the control eye. The 95% confidence interval of IOP change between STB and control eyes was -0.16 to 3.33mmHg (p=0.07). The IOP in normal dogs is reported to vary from 18-22mmHg depending on the time of the day, therefore the degree of alterations in IOP from this study are unlikely to be clinically relevant.(207)

Intraoperative complications encountered included chemosis, miosis and vitreal expansion. Chemosis occurred in a total of 11 cases. The degree of swelling was generally mild and had no impact on surgery. Two cases developed more severe chemosis requiring two small radial perilimbal conjunctival incisions to resolve the corneal coverage by conjunctiva. One case came from the STB group and one from control group. Miosis was only reported as a

complication in the bilateral cataract surgery cases as a small pupil did not affect performance of the other surgeries in this study. Cases that required supplementary intracameral adrenaline for mydriasis were recorded. From the control group 2/12 eyes required intracameral adrenaline, while none of the STB group required intracameral adrenaline. Vitreal expansion syndrome was assessed in the bilateral cataract surgeries in a comparative manner between the STB and control eyes. This variable was assessed with two parameters, vitreal expansion (push), and anterior chamber depth. There was no significant relationship between STB and an increase in vitreal expansion (p=0.15) (Figure 25). Vitreal expansion was deemed to be a true complication in one case, in the STB treated eye. The level of vitreal expansion encountered increased the difficulty placing the intraocular lens implant, but did not prevent successful performance of the surgery.

Figure 25: The number of STB eyes which exhibited either an equivalent (no increase) or an increased level of vitreal expansion when compared to the control NMB eye in the bilateral cataract surgery group.



This data was also tested for correlation between IOP change and increased vitreal expansion (Figure 26). There was no significant relationship between the two factors (p=0.42)

Figure 26: Association between changes in IOP and an increase in vitreal expansion (vitreal push) in the bilateral cataract surgery group to test for a potential link between elevation in IOP and increased level of vitreal expansion.

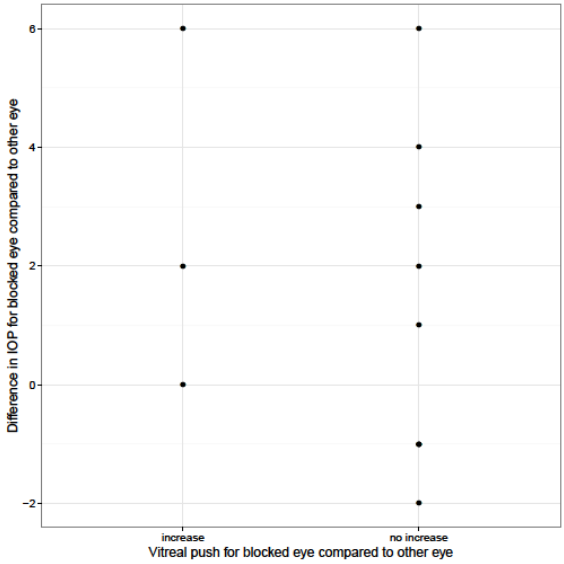
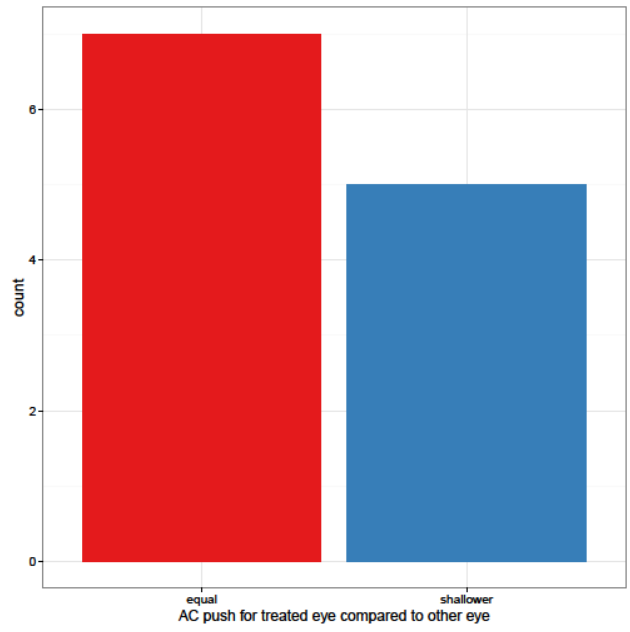
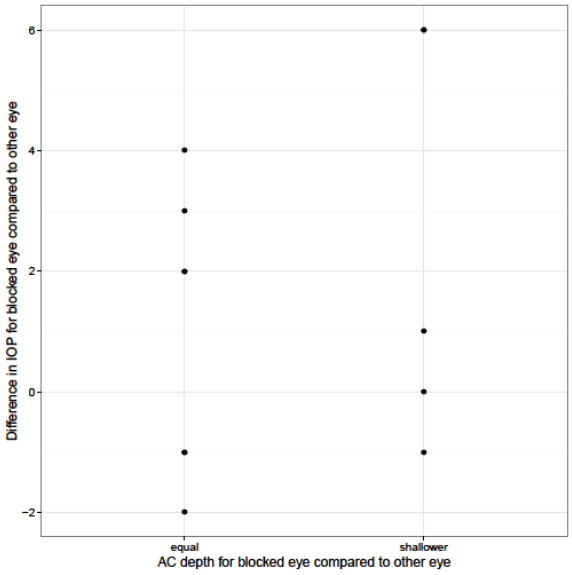


Figure 27: The number of STB eyes which exhibited either an equivalent (equal) or a shallower anterior chamber depth when compared to the control NMB eye in the bilateral cataract surgery group.



Similarly there no significant relationship identified between STB and a shallower anterior chamber (p=0.77) (Figure 27). The data was also tested for a potential correlation between IOP change and shallowing of the anterior chamber, where there was no significant relationship (p=0.31) (Figure 28).

Figure 28: Association between changes in IOP and changes in anterior chamber depth in the bilateral cataract surgery group to test for a potential link between elevation in IOP and shallowing of the anterior chamber



Post-operative complications were recorded for up for two weeks after surgery. Any complications after this time period were assumed to be unrelated to the anaesthetic technique used. The post-operative complications encountered included marked intraocular inflammation, elevated intraocular pressure (>20mmHg), and corneal ulceration. Two cases from the bilateral cataract surgery group had marked intraocular inflammation affecting both eyes. One of these cases had a dental prophylaxis performed at the referring clinic within a week after cataract surgery, which was considered the likely cause of the inflammatory reaction. The cause for the inflammation in the second case was unknown. Both of these cases were successfully managed medically. One bilateral cataract surgery case had an elevated intraocular pressure after surgery in the control NMB eye. This was successfully managed medically. Corneal ulceration occurred in one cataract surgery case which received STB. The corneal ulcer was managed medically, and rapidly resolved without further incidence. One dog which had bilateral cataract surgery was euthanized three days later. This was performed by

the referring veterinarians due to severe pancreatitis developing after surgery. This dogs' systemic illness is unlikely to be linked to the STB, nonetheless this case is reported along with the other complications. It is worth noting that no cases that received STB lost vision after the procedure, from a total of 24 eyes from the cataract and SK surgery groups. All of the complications were grouped together and assessed for a statistical relationship with their treatment group (Figures 29 and 30). There was no significant relationship between STB and post-operative complications (p=0.15).

Figure 29: Proportion of cases with complications in the STB and control groups

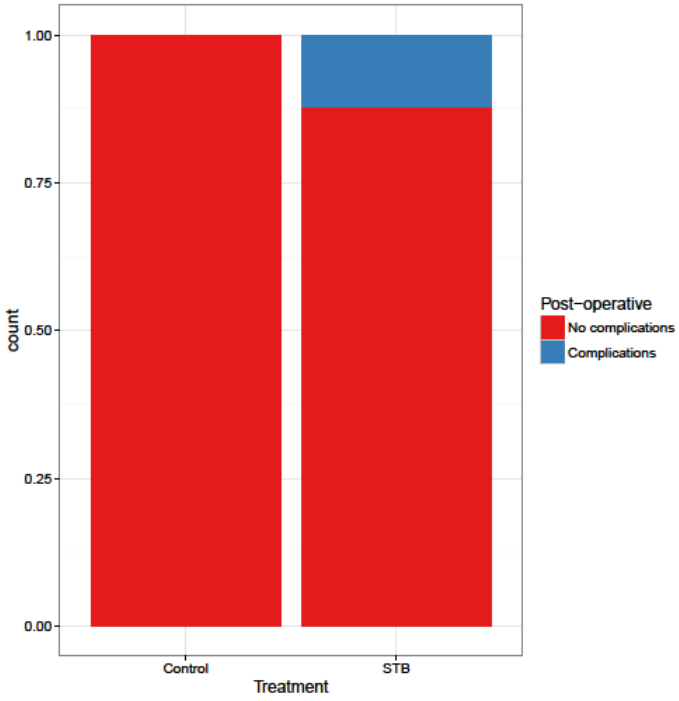
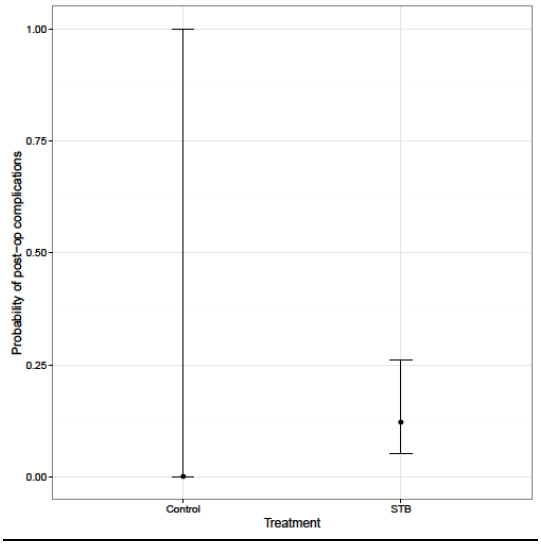


Figure 30: Probability of post-operative complications in the treatment and control groups



Discussion

Sub-Tenon's anaesthesia is a relatively new anaesthetic and analgesic technique for canine ophthalmic surgery. STB has been widely used for human cataract surgery for several years, however it has only been reported in dogs by one group in one small experimental study.(189, 199) The clinical study described herein is the first to report the application of STB in a clinical setting. Once an effective STB technique was developed, the effect was assessed with three key objectives; the effect on analgesia, the suitability of STB as an alternative to systemic neuromuscular blockade for cataract surgery, and identification of any complications associated with STB. To test these effects, the STB technique was used across a variety of patients and surgeries, with many different parameters recorded for assessment. The bilateral cataract surgery cases presented a unique opportunity to compare the effects of STB directly to NMB in a matched pair design. The below sections detail the relevance and application of the study results to clinical canine ophthalmology.

Analgesia

Effective analgesia is a cornerstone for performing surgery in any patient. Assessment of this is challenging in veterinary patients due to the inability to directly communicate, therefore proxy measurements must be used to indicate the level of pain a patient is suffering. This approach is fraught with difficulties, largely due to variations in expression of these factors between patients. The level of pain that the cases experienced in this study were assessed by three

mechanisms; monitoring of parameters during general anesthesia, post-operative pain score testing, and rescue analgesia requirement.

There are many different approaches available to improve intraoperative analgesia, including adjunct regional anaesthesia.(20, 30, 33, 36, 80, 136) A successfully placed STB should render the entire globe desensitised throughout the surgical procedure. It was expected that this would beneficially affect the vital parameters, and reduce the amount of isoflurane required for the procedure. Reducing isoflurane during surgery has significant benefits due to its dose dependent cardiopulmonary depression.(55) This study gathered and assessed the routinely available anaesthetic parameters which did not show a significant difference between STB and control groups. This lack of difference is not entirely surprising as the parameters measured are influenced by factors other than intraoperative nociception and pain. More specific testing modalities like end tidal isoflurane concentration, or serial serum cortisol testing may have shown a difference between the groups, however these techniques were not available for this study.(208, 209) The major finding from this data is that STB does not negatively affect these anaesthetic parameters. This is valuable information for our basic understanding of this new anesthetic technique.

One of the main objectives of this study was to test if use of adjunct orbital local anaesthesia lead to an optimisation of post-operative pain management. It was thought that by pre-operatively anaesthetising the globe with a regional local anaesthetic block, the level of post-operative discomfort would be reduced. This pre-operative local anaesthesia should in theory prevent central sensitisation of nociceptive pathways during surgery and provide analgesia for a period after surgery, facilitating a smooth recovery from anaesthesia and providing time for post-operative NSAID (or other analgesic) to take effect. There was not a clear affect of STB on post-operative pain scores in the non-cataract surgery cases in this study, with only a difference detected in the enucleation group at one time point. This is consistent with findings from other recent orbital anaesthesia studies in dogs undergoing enucleation when adjunct systemic analgesic drugs were used with either a retrobulbar injection or a `splash block`.(31, 32) In addition, systemic carprofen and buprenorphine have both been shown to be effective post-operative analgesics in dogs undergoing a variety of procedures, including enucleation.(35, 210-214) An earlier canine enucleation study with true negative analgesic controls and no systemic analgesia clearly showed the benefit of orbital anesthesia in

controlling post operative pain, with 9/11 control cases required rescue analgesia compared to 2/11 treated dogs.(30) From these studies we can be confident that orbital regional anaesthesia has a significant effect on post-operative analgesia, however this affect is difficult to detect when adjunct systemic analgesics and either retrobulbar injection or `splash block` local anaesthesia techniques are used. Therefore it is not entirely unexpected that this STB study failed to identify a significant difference in post-operative pain scores between the control and STB groups. The slightly lower mean and maximum pain scores in the STB group may indicate a degree of optimisation of analgesia in the STB treated cases. However they could also be the result of more activation of endogenous pain mechanisms as the STB treated cases tended to have higher pain scores before surgery. Due to the variables involved and difficulties associated with subjective pain score assessments, this finding alone does not indicate a definite pattern. Assessment of a larger study population may provide a greater insight into this potential effect.

There was a low requirement of rescue analgesia in this study, with only three of the patients requiring additional medication due to elevated pain scores. One of these was a Staffordshire Bull Terrier, a control case from the superficial keratectomy group. The cause for the behavior changes and elevated pain score in this dog were thought to be due to an adverse response to cage restraint, rather than true pain. Anecdotally, this breed often significantly vocalises when placed in cages in veterinary hospital, both before and after surgery. Post-anaesthetic dysphoria often exacerbates this behaviour, and additional sedation may be required to keep the patient calm and prevent post-surgical trauma from occurring. Regardless of the cause for this elevated pain score, this dog was given additional analgesia, removed from further pain scoring and recorded as a failure of analgesia. The other two patients, a Maltese cross, and a Tibetan spaniel, both had enucleations. Both of these cases were in the control, splash block group. The high pain scores in these patients appear to be a true representation of failure of analgesic technique and a painful post-operative recovery. This shows a higher rate of failure of analgesia with enucleation surgery in the splash block group compared to the STB group, and may indicate that STB provided superior post-operative analgesia for this surgery.

The use of a true negative control without any analgesia was not considered to be an option for this study. Our ethical obligations to provide appropriate care for the patients far outweighed our desire to produce definitive pain scoring results. Fortunately there are previously published studies showing that a lack of analgesia leads to a high rate of rescue analgesia usage in dogs undergoing either enucleation, or cataract extraction.(30, 78) The

information from the study by Mryna et al clearly shows the post-operative analgesic effect of a retrobulbar injection for dogs undergoing enucleation surgery, with only 2/11 retrobulbar block cases needing rescue analgesia, compared to 9/11 cases from the control group.(30)

Recently published enucleation analgesia studies have compared the efficacy of a splash block technique to a retrobulbar injection in dogs in conjunction with systemic analgesics (buprenorphine, hydromorphine, carprofen).(31, 32) These studies used the same pain scoring technique and rescue analgesia threshold to allow comparison to the negative control group from the Myrna et al study. To facilitate usage of all of this information for this STB study, the same pain scoring technique and analgesia thresholds were used. Another recently published study has shown the effectiveness of systemic pre-operative carprofen to provide post-enucleation analgesia in dogs.(35) Combining the information from the previous studies and the findings from this STB study, robust information is produced regarding post-enucleation analgesia, without requiring a negative analgesia control group. Whilst this study was using STB rather than a retrobulbar injection, the local anaesthetic deposition should be in the same intraconal region of the orbit, and therefore have the same analgesic effect.(6, 206) By recognizing this information from previous work, we can be confident that if we had not used analgesics in this study, we would have had a high rate of rescue analgesia usage across at least the enucleation and cataract surgery cases. The remaining surgeries of keratectomy and intrascleral prosthesis (ISP) are likely to be significantly more painful than cataract surgery, and therefore these groups probably would have had a high rate of rescue analgesia usage if they received no analgesia. Based on the information gained in this study, STB provides an excellent level of post-operative analgesia when used in conjunction with systemic buprenophine and carprofen, across a variety of ocular surgeries.

Sub-Tenon' anaesthesia for cataract surgery

Sub-Tenon's anaesthesia is very commonly used to perform cataract surgery in humans. The anaesthesia conditions that STB produce in human patients are also desirable for canine cataract surgery. To test the effects and value of STB in canine cataract patients four main factors were assessed; Mydriasis, globe position, vitreal expansion, end tidal carbon dioxide ($ETCO_2$). STB was used for the bilateral cataract surgery cases in one eye, with the contralateral eye acting as the point of comparison. The order of which eye was operated on was fixed, with the STB eye always being operated on first, followed by the control NMB eye. This ordering

was used to prevent therapies provided for the contralateral eye affecting the assessment of the eye of interest. STB is a regional technique and would likely have no effect on the contralateral eye. The local anaesthetic would either have to diffuse out of the extraocular muscle cone and through the medial bony orbit to affect the contralateral eye, or be given in a dose that would result in systemic effects. Whilst not specifically tested in this study, this lack of contralateral effect is evident from the lack of globe centralisation of the contralateral eye in the cataract surgery cases. In contrast, NMB is a systemic therapy, which would likely have effects on the contralateral eye, and hence may interfere with parameter testing. This approach may confound assessment of the bilateral cataract surgery cases due to the ordering, and the lack of blinding of the surgeon to the treatment group. The author felt that these detrimental confounding effects were outweighed by the improved isolation of effects of individual treatments, resulting in more robust findings.

Pupil dilation (mydriasis) was assessed in all surgery groups to test the occurrence of mydriasis in both the control and STB groups. Whilst the state of the pupil is not clinically significant for performing the non-cataract surgeries, pupil dilation is a pre-requisite for cataract surgery. Assessment of these non-cataract surgery cases showed a very strong association and a very high probability of pupil dilation with STB. This information, while not clinically significant to these groups, provided excellent data on the effects of STB that can be extrapolated to cases where pupillary dilation is a significant consideration. All of the cataract surgery cases received intensive preoperative topical medication (Keterolac, Tropicamide) to achieve pre-operative mydriasis. This protocol prevented isolated assessment of the effects of STB on the pupil. Anecdotally, the STB eyes appeared more dilated than the NMB eyes when the pupils were assessed at the start of surgery for each eye. This is represented in the study data as 0/12 STB eyes required intracameral adrenaline, compared to 2/12 NMB eyes. This apparent reduction in pupil dilation in the NMB eye (which was operated on second) could just be due to the longer time period between completing the topical tropicamide drops and assessment of the pupil (an average of 100 minutes), resulting in some reduction in the mydriatics affect over time. Tropicamide in dogs is reported to produce mydriasis which lasts for 2-12 hours.(82, 215) As the time period between the last administration of topical mydriatic and assessment of the second eye is shorter than the bottom of the reported effective time range, the timing of assessment is unlikely to be the sole explanation of this difference in pupillary dilation. This result suggests an optimized pupil dilation is achieved with STB and the current pre-surgical

drop protocol, compared to pre-surgical drops and NMB. This superior pupil dilation effect of STB compared to NMB is supported with findings from a previous study.(189)

Two aspects of globe position were assessed in this study. Firstly, the presence or absence of rotation away from the central axis andsecondarily, the position of the globe within the orbit. A centrally located globe which is at the level of the orbital rim simplifies surgical positioning and provides good surgical exposure for most ocular surgeries.

It is well established that extraocular muscle akinesia is required for successful cataract surgery.(82) This akinesia has two significant effects; firstly the globe rotates into a central position which maximises visualisation of the intraocular structures, and extraocular muscle tone is abolished which reduces the risk of vitreal expansion during surgery. It has become routine among veterinary ophthalmologists to achieve this effect with systemic neuromuscular blockade.(82, 141, 186, 187) These drugs prevent extraocular muscular contraction by temporarily and reversibly occupying post-synaptic acetylcholine receptors within the neuromuscular junction.(55) The controls in the bilateral cataract surgery group in this study were performed under NMB so a comparison could be made between this new STB technique, and the established routine NMB technique. This study has shown a very high rate of central globe position across all STB treated groups, therefore STB appears to be an excellent option if a centrally rotated globe is desired.

Relative protrusion of the globe can facilitate cataract surgery by improving exposure of the limbal cornea. In deep set eyes, the dorsal orbital rim can interfere with instrument manipulation within the eye, and hence increase the difficulty of surgery. Stay sutures are typically used to fix and pull the eye anteriorly, however this often requires a considerable amount of tension on the conjunctiva and globe, which may increase the risk for vitreal expansion. Retrobulbar injections of saline have been used for this effect in an experimental ophthalmology setting to facilitate ocular positioning for electroretinography.(216) The beneficial effect of forward movement of the globe is most significant in mesaticephalic and dolichocephalic dogs. This study has shown that all globes shift anteriorly after STB which resulted in an improved globe exposure and simplification of surgery in 6/12 cases.

Vitreal expansion is a syndrome where the vitreous body enlarges during cataract surgery. This expansion causes a forward protrusion of the posterior lens capsule which significantly increases the difficulty of cataract surgery. It complicates placement of a prosthetic lens implant, shallows the anterior chamber, increases the risk for iris prolapse, increases the risk of corneal endothelial trauma, and increases the risk of lens capsule rupture during phacoemulsification. This is most commonly a problem in brachycephalic breeds. The vitreal expansion risk is reduced by avoiding external pressure and tension on the globe(from the drape, speculum, clamps and stay sutures), extraocular muscle paralysis (classically through NMB), and occasionally a lateral canthotomy.(141) It is important to take all reasonable measures to prevent this issue from occurring, as it very challenging to manage during surgery can dramatically affect the post-operative outcome for cataract surgery. Vitreal expansion was subjectively assessed in the bilateral cataract surgery cases as being either greater than or equivalent to the control eye. This approach allowed detection of subtle differences between eyes and compensated for individual variation between patients. There were some STB eyes with an increased level of vitreal expansion when compared to the NMB eye, however this difference did not reach statistical significance. Vitreal expansion caused a significant clinical effect in just one case where it was recorded as an intraoperative complication. Clinically there was not a significant difference in the vitreal expansion between the STB and NMB eyes. This shows that STB appears equivalent to NMB for preventing vitreal expansion during cataract surgery.

The capnography results in the non-cataract surgery cases showed significant overlap of results between the STB and control groups. This data set shows that STB usage is not detrimental to capnography when compared to standard general anaesthesia procedures. STB was compared to systemic neuromuscular blockade (NMB) in the bilateral cataract surgery group. NMB has dose dependent effects on all skeletal muscles including those involved in respiration. This often causes respiratory depression, reduction in tidal volume, hypercapnia, respiratory acidosis and hypoxia.(185, 187, 188) This bilateral data showed a trend of higher $ETCO_2$ in the NMB eyes, however this did not reach statistical significance. It is fair to assume that if a higher dose NMB agent was used, there would be a significant difference in either the capnography results or the requirement for mechanical ventilation. The findings from this data suggests that STB may be superior to the low dose NMB technique used in this study in minimising the effect of general anaesthesia and cataract surgery on $ETCO_2$. There are other potential factors that could account for an elevated $ETCO_2$ in the NMB eye group. As the NMB

eye was always the second eye operated on, the measurements were taken after a previous period of general anaesthesia (around 100 minutes), and after the patient has been repositioned for surgery on the second eye. This combination of affects may result in ventilation-perfusion mismatch due to atelectasis in the previously dependent lung lobe.(55, 217) This could theoretically affect $ETCO_2$, although this may be more important in species larger than the dogs in this study.(55, 218, 219)

Sub-Tenon's block was shown to achieve all of the required surgical conditions necessary for canine cataract surgery. These comparisons were made against eyes receiving NMB and therefore providing good information about the effects of STB directly compared to NMB. STB is a good option for these cases and has the potential to replace systemic neuromuscular blockade as the standard practice for canine cataract surgery.

Complications

Complication identification was an important aspect of this study. STB is a new technique and without information about the issues identified with its' application, the uptake of this technique across the profession would be low. Complications were recorded for both STB and control cases receiving non-cataract surgery. For the bilateral cataract surgery cases, the eye(s) with the complication were recorded and identified whether they were in the STB or NMB group. Complications were recorded at three points: at block placement, intraoperatively, and post-operatively.

The complications encountered at STB placement included STB failure and episcleral haemorrhage. IOP elevation after STB placement was considered to be possible; therefore this was monitored as a potential complication at this stage. The two dogs which had a failure of STB technique were noted to have a very thick and robust Tenon's capsule. This made sub-Tenon's tunnel creation difficult, and prevented passage of the cannula into sub-Tenon's space. When the local anaesthetic was infused, it was deposited intra-Tenon's. This misdirection of local anaesthetic away from the intraconal region resulted in an ineffective block, due to the extraocular muscles and associated motor nerves not being exposed to the local anaesthetic solution. In addition the misdirected fluids caused significant chemosis. The two cases of episcleral haemorrhage had significant pre-existing ocular disease with engorged episcleral vessels. These vessels would have been more susceptible to trauma and

haemorrhage during the creation of sub-Tenon's tunnel.(82) In human studies minor haemorrhage occurs in 7-46% of cases, with 0.1% having significant haemorrhage which impacts surgery.(174) As both of these eyes were enucleated, we cannot show that this complication did not affect the long term health of the eye. However the author speculates that due to the severity of haemorrhage and the rapid self-resolution, it is likely that these eyes would have not been adversely affected after surgery. Intraocular pressure (IOP) measurements were performed immediately prior to STB block placement, and immediately afterwards to detect any changes in IOP as a result STB. Measuring the IOP at these stages should highlight the maximal IOP elevation, as the IOP tends to decrease with time after STB.(162, 163) There was a tendency of IOP elevation in the STB eye in the bilateral cataract surgery group, though this did not reach statistical significance. This IOP elevation was not clinically significant as the 95% confidence interval showed a pressure elevation of ≤ 3.33mmHg as normal diurnal variation IOP in dogs is around 4mmHg.(207) In the authors' opinion, an IOP elevation of the level found in this group would not significantly affect the ocular health in any of our surgical cases. In addition there was no association found between elevation of IOP and the presence of vitreal expansion. This interesting finding suggests that IOP elevation post-STB is a poor indicator of vitreal expansion, and hence subtle pre-operative IOP elevations may not precipitate intraoperative complications.

Three types of complications were encountered intraoperatively; chemosis, miosis and vitreal expansion. Chemosis can occur when local anesthetic solution diffuses under the conjunctiva after STB. This is a common occurrence with STB in humans, with a reported occurrence of mild chemosis between 5.6-40%.(9, 90, 109, 174) It is important to recognize that this rarely affects surgery, with only 0.06% patients having a more difficult surgery due to chemosis.(9) This canine STB study showed that mild chemosis occurred in 30% of STB cases (10/33 STB cases). Significant chemosis occurred in 1 STB (3%) and 1 control dog (3%). This complication was quite simply treated by two small radial perilimbal conjunctival incisions. This resolves the hooding effect of the swollen conjunctiva over the perilimbal cornea, and surgery was not detrimentally affected. Some dogs appear to have very reactive conjunctiva which rapidly swells upon surgical stimulation. This explains the one case from the control group with this complication. Miosis was recorded as a complication only in the cataract surgery cases, as a small pupil has no effect on the performance of the non-cataract surgeries. Intraoperative miosis was encountered in two eyes from the control NMB group. This miosis was treated with intracameral adrenaline to provide mydriasis so cataract extraction surgery could be

performed. This low number of cases is not enough to indicate a trend, however anecdotally eyes which received STB appear to have more dilated pupils than the NMB eyes. As more cataract surgeries are performed under STB, this superior mydriatic effect may become more apparent. Vitreal expansion was encountered in one STB bilateral cataract surgery case. As this vitreal expansion tendency doesn't appear to be correlated to changes in IOP after block placement, the author suspects that the vitreal expansion is related to anterior movement of the globe from volume displacement with the STB infusion. This may result in compression of the globe against the internal surface of the palpebral fissure, particularly in breeds with a tight lid conformation. This was thought to be the most likely cause of the issue in the bilateral surgery case which was a small 5kg Australian terrier with a tight eyelid conformation.

Post-operative complications were uncommon in this study, with only 5 cases recorded as having a complication within 14 days of surgery. When intraocular inflammation occurred in two cases, it affected both the STB and control eye. The one eye with an IOP elevation was a control NMB eye, and the one corneal ulcer was a STB eye. From this data, the main concern that may arise with STB usage is post-operative corneal ulceration. Ulcers may occur after cataract surgery due to exposure during the recovery period in the first day or so post-operatively. Post-operative ulceration is likely caused from corneal exposure due a combination of factors including lagophthalmos following general anaesthesia, and fatigue of orbicularis oculi muscle after eyelid speculum usage. To help prevent this, human cataract patients are often discharged with an eye patch for one day after surgery (Dr Helen Long personal communication). STB may increase the risk for ulceration by exacerbating corneal exposure via two mechanisms; prolonged corneal desensitization after surgery reducing the stimuli to blink, and reduced corneal coverage by the eyelids due to forward movement of the globe. None of the dogs in this study (26 cases) which received a STB lost the ability to blink, therefore the ulceration was not caused by eyelid akinesia. The few dogs that developed ptosis after extubation all self resolved before discharge. Regardless, dogs receiving this STB technique may be a higher risk for developing post-operative corneal ulceration.

Simple alterations to the STB technique are likely to greatly reduce the risk of the complications reported. Accurate dissection, and cannula placement beyond the globe equator should prevent block failure, and reduce the risk of chemosis.(90) For eyes with engorged episcleral blood vessels, extra care should be taken during dissection to prevent haemorrhage from occurring. A lower volume STB should further reduce any IOP elevation post-block, reduce the risk of chemosis, help prevent vitreal expansion, and corneal exposure from

relative exophthalmos.(162, 163) Use of lubricating ointments or a lateral temporary tarsorraphy after STB may also prevent corneal decussation and ulceration, particularly in shallow orbited breeds that are higher risk of corneal exposure.

Overall this study has shown that STB has a low level of associated complications. Simple alterations to the technique and post-operative management are likely to reduce this complication rate even further. Therefore from a safety point of view, STB is a legitimate option for canine ophthalmic surgery.

Limitations of the study

As with any clinical study, there are limitations to the level of control and manipulation that can be performed on the subjects, this study is no exception. The most important limiting factors are discussed below.

The cases assessed were of varying signalment, belonging to several breeds, of varying age and sex, with a variety of surgical procedures performed. This variation is likely to affect the comparisons made between individuals and groups, particularly regarding post-operative pain scoring. This varied population distribution is fairly representative of the surgical cases seen in our clinic and allows assessment of the procedure across a wide variety of types of dog. Whilst this lack of standardisation complicates the comparisons that are able to be performed, there is significant benefit in this data representing a clinical population. This is likely to increase the relevance of this study's findings to clinical veterinary ophthalmologists.

Significant effort was made to standardise the anaesthetic and surgical techniques used in the cases. There was however an expected level of variation as these were tailored to meet the patient’s requirements. These alterations involved a minority of the cases (e.g. the percentage of cases not receiving post-operative acepromazine was 17%). The author feels that these changes would not have significantly affected the results.

The rationale for the lack of true negative controls has been previously discussed. This alters the point of comparison for many of the variables and hence complicates assessment of the

findings. Due to the previous studies with negative analgesic controls, and knowledge of the effects of NMB on cataract surgery, meaningful assessment of outcomes in the STB study could be made, even with the absence of true negatives in this study.

All patients in this study were managed as day surgery cases, with varying surgery times, and discharge times throughout the day. This resulted in an inconsistent length of hospitalization after surgery, and a variable length of post-operative pain score monitoring. Overnight hospitalization simply to extend pain scoring for this study, was not in the patients' interest. Many clients drive several hours to reach the clinic as it is the only veterinary ophthalmic clinic in South Australia. If an overnight stay was made a prerequisite for inclusion into the study, it would have been very difficult to enroll enough cases to develop any information. Previous studies performed have shown a relatively short time to analgesia failure post-operatively for enucleation surgery.(30-32, 78) Across all of these studies, the mean time to analgesia failure was 46.9 minutes, with a range of 0-240 minutes. This is an interesting finding which is currently unexplained, however it may be associated with up-regulation of endogenous analgesic pathways which control post-operative pain following removal of a chronically painful globe. With this information, we can assume that in this study the vast majority of failures of analgesia would have been detected within the post-operative pain scoring period. There is a risk that some cases had a late failure of analgesia technique that would have been undetected by this study. Therefore there is some risk that the true incidence of failure of analgesia has been underrepresented. This period of assessment could have been extended by requesting owners to perform pain scoring at home for the first few days after surgery. Whilst this would have provided more data, it will have likely introduced significant bias of assessment with untrained observers, and would only complicate assessment of findings in this study. This study utilized different trained observers to record pain scores across the cases. Ideally a single blinded observer would have been used across all of the cases to minimise the intra-case and inter-case variation. This was not possible due to staffing levels and the other staff responsibilities that occur in clinical practice. Multiple observers would likely confound the results to some degree. Each individual case was managed by a single observer from the beginning to the end of pain scoring to minimise the intra-case variation of recorded pain scores. Due to the pain scores across all groups being generally low, this inter-case variability may not have significantly affected the results and conclusions which were drawn. Regardless, the effect of multiple assessors may have contributed to the lack of

difference in pain scores found between the groups in this study and must be considered when evaluating these post-operative pain score results.

The unblinded and subjective nature of assessments for vitreal expansion and globe position within the orbit are clearly a potential source for bias and inaccurate reporting of results. Blinding the assessor for these parameters would complicate anaesthesia management, and would likely require abandonment of the matched pairs design. This would significantly detrimentally affect the relevance of these results. Utilizing a matched pair design and simplifying the data assessment should improve the validity of these results and reduce to potential effect of bias of assessment.

The data produced from this study showed the high rate of successful STB placement, with production of good surgical conditions and a very low rate of complications. Therefore highly valuable information was gathered from this study, despite the limitations discussed above.

Future study

Further clinical and experimental studies assessing STB will provide a greater understanding of the benefits, limitations and contraindications. A summary of potential future studies is listed below:

- Assessment of the affects of varying volumes of STB depending on dog size and orbital conformation.
- Testing of higher concentration bupivicaine (0.5%) at lower volumes for the small breed dogs
- Determining the mydriatic effects of STB in experimental and clinical cases, and the suitability for cataract surgery.
- A prospective clinical study assessing post-operative pain after intrascleral prosthesis surgery with different analgesia treatment groups.
- As this study has shown that sub-Tenon's anaesthesia is a safe and effective technique, larger clinical studies can now be conducted with confidence. This will provide a wider data set for assessment which veterinarians can draw from.

Conclusion

Orbital regional anaesthesia has many beneficial effects on operating conditions and analgesia in a variety of species undergoing ophthalmic surgery. Sub-Tenon's anaesthesia has become a popular technique in human ophthalmology where it has resulted in a shift away from retrobulbar and peribular injection and general anesthesia for cataract surgery. A safe and effective STB technique was developed for use in dogs that was subsequently tested in a clinical population across a variety of ophthalmic surgeries. This showed that STB provided post-operative analgesia that was at least as good as the standard practice for analgesia used in our clinic. STB was an excellent alternative to systemic neuromuscular blockade in cataract surgery cases. This finding could result in a shift away from NMB in veterinary ophthalmic clinics as there are many benefits to using STB under general anaesthesia compared to NMB. The level of complications encountered with STB usage was low and not significantly different to the control group. It is likely that the complications encountered can be reduced further with refinement of the STB technique as more studies are performed. In summary, sub-Tenon's anaesthesia was shown to be an excellent technique for canine ophthalmic surgery and provides a new option for veterinary ophthalmologists and anaethetists.

Declaration of interest

The author has no financial interests in the techniques and materials utilized in this study that could have influenced the submitted work.

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Appendices

Appendix A: Rationale for excluding specific surgical cases from the study

Surgical cases excluded	Rationale
Eyelid surgery	Block placement would likely have minimal effect on the sensory and motor nerves in this region
Nictitans surgery	These surgeries seem to be minimally painful, and block placement would not impact surgery
Intracapsular lens extraction surgery for lens luxation	Complete pupil dilation pre-surgery was often not indicated, due to the risk of an anterior luxated lens moving posteriorly
Deep or perforated corneal ulcer	Minimal pre-surgical handling was indicated to reduce the risk of pre-operative globe rupture
Infected corneal ulcers or severe ocular surface infection	Avoid the risk of seeding infection behind the globe due to cannula placement
Corneal grafting cases	If the graft was to be harvested from the dorsolateral conjunctiva, pre-operative block placement would impact the graft creation due to the conjunctival incision and sub-Tenon's tunnel
Very old or very sick dogs	Every effort was made to minimise anaesthesia length, including omitting block placement
Ocular surface neoplasia	When there was a risk of seeding neoplastic cells into the orbit due to the block, cases were not included
Retrobulbar neoplasia	Minimise the risk of seeding tumour deeper into the orbit

Appendix B: Premedication Acepromazine dosing schedule

Weight range	Acepromazine dose
0-10kg	0.025mg/kg
10-20kg	0.015mg/kg
>20kg	0.01mg/kg

Appendix C: Exclusion criteria for post-operative ACP

Boxer or sight hound breeds

Dogs with epilepsy

Very aged dogs

Dogs with significant pre-existing systemic disease; i.e cardiac, hepatic, renal

Cases with a prolonged recovery period to extubation

Cases with persistent periods of low blood pressure during surgery (mean arterial pressure < 60mmHg)

Appendix D: Pain scoring system used in this study

Pain score table

Characteristic	Score	Criteria
Comfort	0	Asleep or calm
	1	Awake and interested in surroundings
	2	Mild agitation or depressed and uninterested in surroundings
	3	Moderate agitation, restless, and uncomfortable
	4	Extremely agitated or thrashing
Movement	0	Quiet
	1	1-2 position changes per minute
	2	3-6 position changes per minute
	3	Continuous position changes
Appearance of tx eye	0	Normal
	1	Mild changes (affected eye partially closed
	2	Moderate changes (blinking or third eyelid protrusion of affected eye)
	3	Severe changes (affected eye continuously closed or pawing at eye)
Behaviour unprovoked	0	Too sedate to evaluate
	1	Normal
	2	Minor changes
	3	Moderately abnormal (less mobile or alert than normal, unaware of surroundings, or restless)
	4	Markedly abnormal (very restless, vocalising, self-mutilating, grunting, or facing the back of cage)
Interactive behaviours	0	Too sedate to evaluate
	1	Normal
	2	Pulls away or blepherospasm when surgical site touched; mobile
	3	Vocalises when wound touched and reluctant to move but will when coaxed
	4	Violent reaction to touching of sx site, snapping, growling when approached, or failing to move when coaxed
Vocalisation	0	Quiet
	1	Crying but responds to quiet voice and stroking
	2	Intermittent crying, with no response to quiet voice and stroking
	3	Constant crying (unusual for this particular dog), with no response to stroking or voice
Palpebral reflex	Y	Positive when stimulated
	N	Negative when stimulated

Adapted from: *Park SA, Park YW, Son WG et al*. Evaluation of the analgesic effect of intracameral lidocaine hydrochloride injection on intraoperative and postoperative pain in healthy dogs undergoing phacoemulsification. **American Journal of Veterinary Research**. 71(2), 216-222. 2010.

Appendix E: Pain score recording data sheet

Pain scale recording

Assessor initials:

Case number: Age: Breed/sex: Weight: Eye affected: Diagnosis: Surgical procedure: Time premed:

Time induction: Time extubation: ST block dose and volume: Eye position at surgery/pupil: Pre block IOP: Post block IOP:

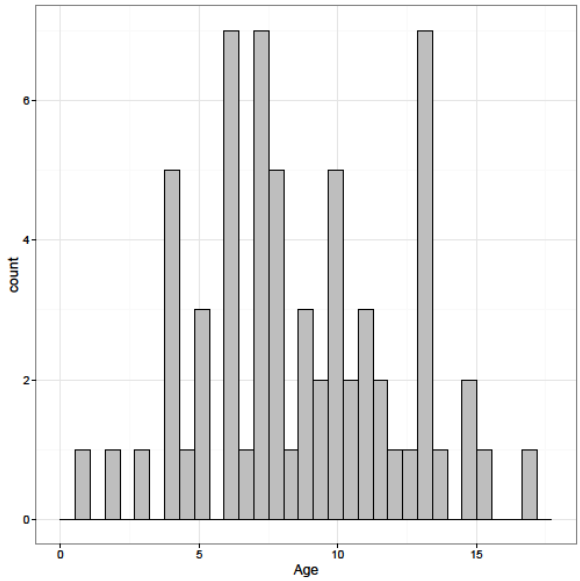
Time of post op rimadyl: Time post op ACP: Time rescue analgesia?: Adverse effects?:

TIME	Pre	0	15	30	45	60	90	120	150	180	240	300	360
Comfort													
Movement													
Appearance of tx eye													
Behaviour unprovoked													
Interactive behaviours													
Vocalisation													
Palpebral reflex													

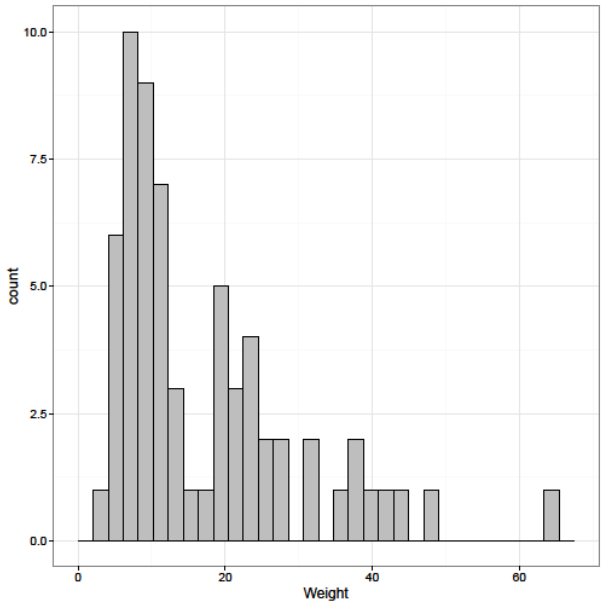
Notes:

Characteristic	Score	Criteria
Comfort	0	Asleep or calm
	1	Awake and interested in surroundings
	2	Mild agitation or depressed and uninterested in surroundings
	3	Moderate agitation, restless, and uncomfortable
	4	Extremely agitated or thrashing
Movement	0	Quiet
	1	1-2 position changes per minute
	2	3-6 position changes per minute
	3	Continuous position changes
Appearance of tx eye	0	Normal
	1	Mild changes (affected eye partially closed
	2	Moderate changes (blinking or third eyelid protrusion of affected eye)
	3	Severe changes (affected eye continuously closed or pawing at eye)
Behaviour unprovoked	0	Too sedate to evaluate
	1	Normal
	2	Minor changes
	3	Moderately abnormal (less mobile or alert than normal, unaware of surroundings, or restless)
	4	Markedly abnormal (very restless, vocalising, self mutilating, grunting, or facing the back of cage)
Interactive behaviours	0	Too sedate to evaluate
	1	Normal
	2	Pulls away or blepharospasm when surgical site touched; mobile
	3	Vocalises when wound touched and reluctant to move but will when coaxed
	4	Violent reaction to touching of sx site, snapping, growling when approached, or failing to move when coaxed
Vocalisation	0	Quiet
	1	Crying but responds to quiet voice and stroking
	2	Intermittent crying, with no response to quiet voice and stroking
	3	Constant crying (unusual for this particular dog), with no response to stroking or voice
Palpebral reflex	Y	Positive when stimulated
	N	Negative when stimulated

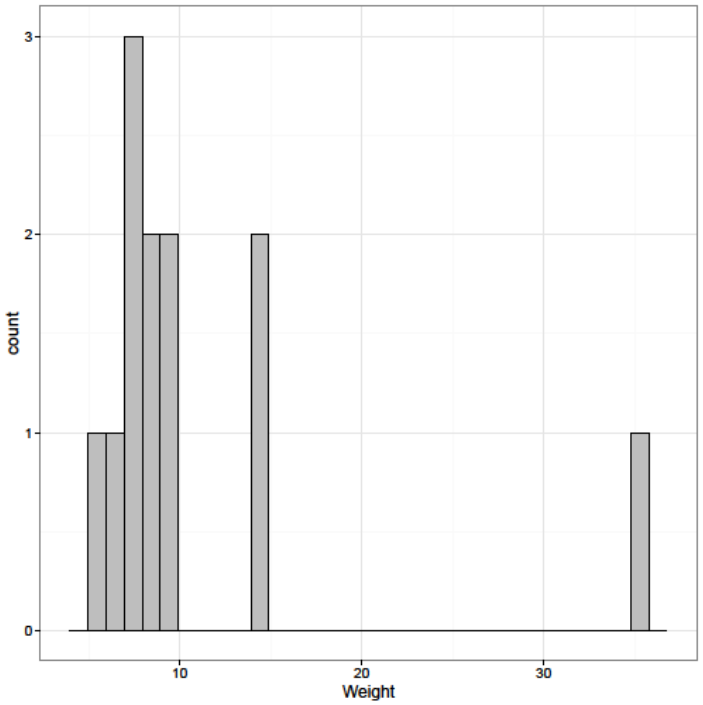
Appendix F: Age distribution of the dogs involved in this study



Appendix G: Body weight distribution for non-cataract surgery cases



Appendix H: Body weight distribution for bilateral cataract surgery cases



Appendix I: Breeds represented in the study population.

Breed	**Number**
Maltese cross	11
Boxer	5
Labrador Retriever	4
Terrier cross	4
Staffordshire Bull Terrier	3
Border Collie	2
Jack Russell Terrier	2
Australian Terrier	1
Bichon Frise	1
British Bulldog	1
Bull Mastiff	1
Cavalier King Charles Spaniel	1
Cocker Spaniel	1
Great Dane	1
Kelpie	1
Kelpie x	1
Labrador cross	1
Miniature Schnauzer	1

Miniature Short Haired Fox Terrier	1
Pug	1
Rottweiler	1
Shar Pei	1
Shetland Sheepdog	1
Shiba Inu	1
Shih Tzu	1
Siberian Husky	1
Soft Coated Wheaten Terrier	1
Tibetan Spaniel	1
West Highland White Terrier	1
Whippet	1