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Evaluation of a Modified Infraorbital Approach for a Maxillary Nerve Block for Rhinoscopy with Nasal Biopsy of Dogs

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A maxillary nerve block via a modified infraorbital approach, applied before rhinoscopy and nasal biopsy, would decrease nociception, minimize cardiorespiratory anesthetic effects, and improve recoveries. In a crossover study, bupivacaine or equivalent volume of saline was administered to 8 healthy dogs via a modified infraorbital approach into each pterygopalatine region. Rhinoscopy and nasal biopsy were performed. Heart rate, blood pressure, plasma cortisol and norepinephrine concentrations, purposeful movement, and pain scores were monitored. Following a 14-day washout, dogs received the alternate treatment on the contralateral side. Blood pressures were significantly higher for the saline treatment than bupivacaine treatment. Plasma cortisol concentrations in the saline treatment were significantly higher 5 minutes after biopsy than at biopsy. No other parameters were significant. Using a maxillary nerve block via a modified infraorbital approach prior to rhinoscopy and nasal biopsy reduced procedural nociception. These findings warrant further evaluation in dogs with nasal disease.

DEDICATION

I would like to dedicate this work to all of my mentors, family, and friends who have been there for me, supported me through every endeavor, and shared their tidbits of wisdom. I would not have been able to do this without your help and guidance, it means the world to me.

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CHAPTER I

INTRODUCTION

Nasal diseases are common in small animal patients, and rhinoscopy with nasal biopsy has become the gold standard procedure for evaluation and diagnosis of nasal diseases in the dog.[1,2] Unlike human patients, our animal patients require general anesthesia for endoscopic procedures, carrying with that, potential risks associated with an anesthetic event.[3] Multimodal anesthesia, incorporating the use of many different treatment modalities, provides the safest anesthesia and has become the gold standard for anesthetizing patients with greater risk for anesthetic complications.[4] Careful study of the innervation of the face and nose in the dog and human has provided insight into the use of regional nerve blocks and local anesthetics to desensitize the nasal cavity. This may provide benefit to the patient with long lasting effects, minimizing the anesthetic complications, and providing a better recovery following rhinoscopy with nasal biopsy or other painful invasive procedures.

Rhinoscopy with nasal biopsy

Canine nasal diseases, which include a variety of inflammatory, infectious, and neoplastic processes, are a common cause for sneezing and nasal discharge in the dog.[2] Differentiating between the multiple disease etiologies is paramount, as the treatment for each disease process is different and often tailored. Historically, many nasal disease processes would require an invasive surgical technique in order to obtain the diagnosis or

the use of non-invasive techniques with a low diagnostic yield.[5] The use of endoscopy to visualize areas of the nose that are not available to the naked eye have made procedures in human and animal medicine less challenging over the past several decades.[5] Rhinoscopy involves the use of a rigid fiber optic camera to visualize the contents of the nasal cavity via the nares, and a flexible fiber optic camera to visualize the caudal nasopharynx via the mouth by retroflexing the camera around the caudal aspect of the soft palate dorsally.[6] With new technology comes new concerns. Rhinoscopy is a very stimulating procedure to the internal structures of the nose and often causes patients to develop a sudden light plane of anesthesia, with accompanying head shaking, gagging, swallowing, sneezing, and chewing. The nasal mucosa is very sensitive to touch, and introduction of the scoping equipment into the nasal cavity can cause sudden stimulation and patient movement. Since our animal patients require general anesthesia for endoscopic evaluations, these patients must be kept at a deeper anesthetic plane to prevent movement, thus minimizing the risk of trauma and injury to the patient, and damage to expensive endoscopy equipment. Associated with a deeper plane of anesthesia is a greater likelihood of cardiorespiratory complications such as apnea and hypotension.[7]

Anesthesia

With any general anesthetic event, there are inherent risks associated, especially in patients with underlying disease processes.[8-10] Recent literature on anesthetic mortality in dogs was measured at 0.17%, with 0.05% in healthy dogs, increasing to 1% in patients with more severe systemic disease processes.[11] The American Society of Anesthesiologists (ASA) developed a classification system in humans which has been adapted and widely accepted into veterinary medicine, categorizing patients based upon

their disease process and physical health status. In this system, patients with a higher ASA classification have a greater risk of anesthetic associated death.[12,13] Dogs undergoing rhinoscopy with nasal biopsy procedure are often of a higher ASA classification, as they are presenting with a disease process that requires rhinoscopy with nasal biopsy, increasing the anesthetic risk to these patients as compared to a normal healthy patient. Chronic and systemic disease processes increase the risks associated with anesthesia, increasing complication rates seen during and perioperatively.[11] Inhalant anesthetics cause a dose-dependent cardiovascular depression, resulting in decreased cardiac output and hypotension.[14] To help make the anesthetic event for diagnostic procedures the safest for the animal, multimodal or balanced techniques have been adopted. These include many different treatment modalities offering many of the benefits of drug combinations at lower doses, while limiting the side effects of a single drug used at a high dose, to provide the anesthesia and analgesia required to perform an invasive and painful diagnostic procedure in the veterinary patient.[15,16] A variety of different drugs and techniques can be included, such as opioids, injectable anesthetics, α-2 adrenergic agonists, NMDA antagonists, NMBAs, and local anesthetics, in addition to inhalant anesthesia.[17] The value of balanced anesthesia has been studied extensively, and its use has a significant additional benefit in the post-operative period.[18] The control of post-operative pain, better comfort of patients in recovery, and the ability to rest and heal is paramount. This can be achieved by preventing pain via a multimodal analgesic approach in the recovery period, decreasing the perioperative stress levels and allowing the body to heal.[4,19]

Stress response

A stress response occurs any time there is trauma or injury, and is associated with anesthesia and surgery.[20] Hormonal and metabolic changes take place in response to these stressors. Increased corticotrophin release from the pituitary gland stimulates the release of cortisol from the adrenal cortex, and activation of the autonomic sympathetic nervous system by the hypothalamus increases release of norepinephrine from presynaptic nerve terminals.[21] In clinical patients, an increase in the sympathetic nervous system response manifests as cardiovascular effects such as increased heart rate, respiratory rate, and blood pressure, which can be caused by anxiety, trauma, pain, or a nociceptive stimulus. In wild animals, stress responses have developed to allow injured animals to survive without showing overt signs of illness.[20]

Plasma catecholamine concentrations can be a useful indicator of stress and nociceptive stimulation occurring in human and veterinary patients.[22] Following a stressful event, plasma norepinephrine concentrations increase immediately, whereas plasma cortisol concentrations can take up to 4-6 hours for increases to be seen.[23,24] In several surgical studies, catecholamine measurement was used as a definitive method to determine effectiveness of analgesic and balanced anesthesia protocols, in comparison to general post-operative comfort via a pain scoring questionnaire. In some orthopedic patients, no differences in pain scoring was noted, though decreases in plasma cortisol concentrations were seen.[25] In pediatric patients, epidural anesthesia decreased the catecholamine stress response more significantly that opioids alone.[26] In dogs undergoing repeated noxious stimuli, increased plasma cortisol levels correlated to increases in surgical stress.[27]

Anatomy of the nose

The nasal cavity, which contains the primary sensory organ in the dog, is very sensitive and contains an intricate network of nerves that would make rhinoscopy a painful procedure in an awake animal. Rhinoscopy is also very stimulating in an anesthetized animal, and makes for difficult analgesia in the dog. The nose is complex, both in structure and function, providing olfaction, as well as humidifying, warming, and filtering of inhaled air.[28] Understanding the anatomy of the dog face and nose can provide insight into the development and use of techniques allowing the use of regional nerve blocks to anesthetize areas of the face and nose, providing antinociceptive properties for painful and invasive diagnostic procedures.

Though there are many distinct differences between the human and canine facial anatomy, there are many strong similarities.[29] The cranial nerves serve many of the same primary functions in the human and dog, as they do in all mammals, though the nasal anatomy of the dog is more pronounced and of greater importance to the dog than the human.[30] One of the major differences in the human and dog nasal anatomy is that dogs are macrosmats, using the nose for primarily olfaction, with higher levels of olfactory function, while humans are microsmats, using the nose primarily for breathing.[28,29,31] Dogs have much larger and complex turbinate structures with a greater olfactory area than that of the human,[32] though nerve anatomy and physiology, especially that of the trigeminal nerve, remains much the same.[33] Comparative anatomy of the man, dog, and other species has shown that despite differences in appearance and function, the developmental origin of the trigeminal nerve, and its function, has remained the same.[34]

The trigeminal nerve

Cranial nerve V, the trigeminal nerve, is the largest of all the cranial nerves, dividing into three branches providing motor, sensory, and autonomic innervation the structures of the face. Though the trigeminal nerve itself does not provide autonomic innervation, it does communicate and travel with autonomic fibers from the oculomotor (cranial nerve III), facial (cranial nerve VII), and glossopharyngeal (cranial nerve IX) nerves to collectively provide autonomic innervation to lacrimal, nasal, and salivary glands.[35-37] The trigeminal nerve exits the brainstem entering trigeminal canal, where the sensory trigeminal ganglion resides. Distal to the trigeminal ganglion, the trigeminal nerve separates into its three branches: the ophthalmic (V1), maxillary (V2), and mandibular (V3) nerves, each providing a range of innervation to its associated areas of the face (Figure 1.1).[38]

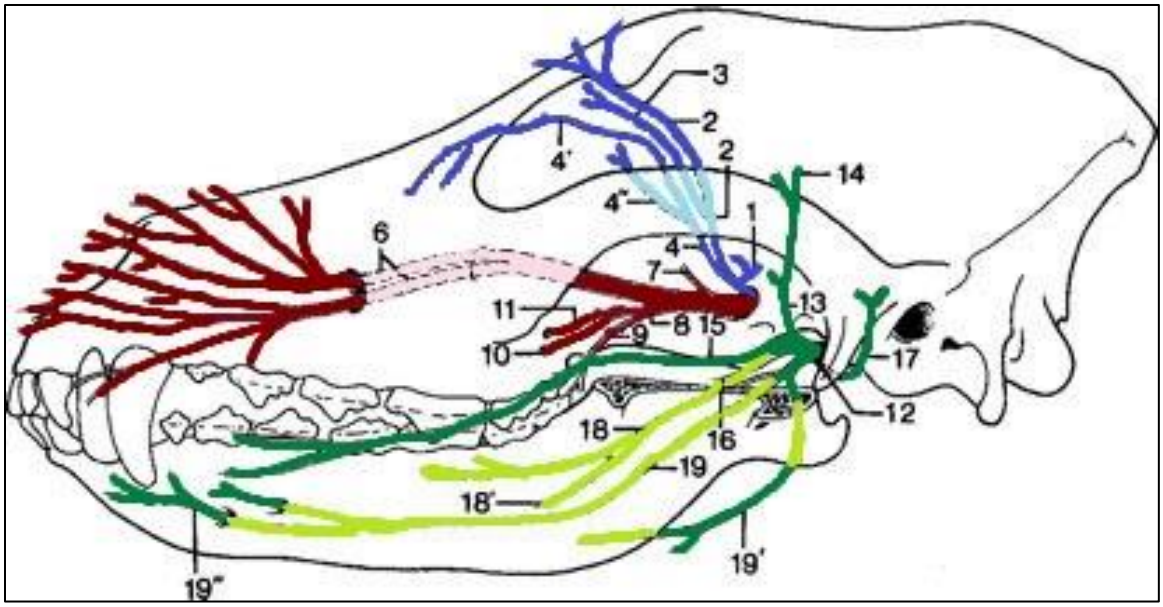

Figure 1.1 The trigeminal nerve.

Illustration adapted from Dyce, Sack, and Wensing. Textbook of Veterinary Anatomy, 3rd edition. The ophthalmic nerve and its branches (V1, in blue). 1, ophthalmic n.; 2, frontal n.; 3, lacrimal n.; 4, nasociliary n.; 4', infratrochlear n.; 4", long ciliary n. The maxillary nerve and its branches (V2, in red). 5, maxillary n.; 6, infraorbital n.; 7, zygomatic n.; 8, pterygopalatine n.; 9, lesser palatine n.; 10, greater palatine n.; 11, caudal nasal n. The mandibular nerve and its branches (V3, in green). 12, mandibular n.; 13, masticatory n.; 14, deep temporal n.; 15, buccal n.; 16, pterygoid n.; 17, auriculotemporal n.; 18, lingual n.; 18', sublingual n.; 19, inferior alveolar n.; 19', mylohyoid n.; 19", mental n.

The ophthalmic nerve (V1)

Distal to the trigeminal ganglion, the first branch of the trigeminal nerve, the ophthalmic nerve, emerges from the cranial vault through the orbital fissure. The branches of the ophthalmic nerve provide sensory innervation to the eyelids, eyeball, nasal mucosa, and skin of the nose. The ophthalmic nerve divides three main branches, the lacrimal, frontal, and nasociliary nerves. The lacrimal nerve innervates the skin of the lateral canthus of the eye. The frontal nerve divides into the supraorbital and supratrochlear nerves, innervating the cutaneous area on the lateral two-thirds of the

upper eyelid and continuing to dorsal midline, innervating the bone and mucosa of the frontal sinus. The nasociliary nerve branches into the infratrochlear, ethmoidal, and long ciliary nerves, providing innervation to the medial canthus of the eye and the frontal sinus, the septum and wall of the nasal cavity, and the sensitive tissues of the eyeball, cornea and bulbar conjunctiva, respectively.[36,38]

The lacrimal nerve associates with and carries the postganglionic parasympathetic fibers of the facial nerve (from the pterygopalatine ganglion) to provide innervation to the lacrimal gland.[39] The nasociliary nerve communicates with the ciliary ganglion to form the short ciliary branches of the oculomotor nerve with post ganglionic sympathetic fibers from the cranial cervical ganglion supplying three smooth muscles groups in the orbit: the third eyelid retractor, the smooth muscle bands pulling the eyeball rostrally, and the pupil dilator.[36,37]

The maxillary nerve (V2)

The maxillary nerve exits the cranial vault through the round foramen, running across the pterygopalatine fossa ventral to the orbit rostrally toward the infraorbital foramen and branching into several different nerves that provide sensory innervation to the lower eyelid, nasal mucosa, upper teeth, upper teeth, and nose. The maxillary nerve has three main branches: the zygomatic, pterygopalatine, and infraorbital nerves. The zygomatic nerve branches into the zygomaticofacial and zygomaticotemporal nerves, innervating the lower eyelid, medial and lateral canthi of the eyes, and the cutaneous area dorsal to the zygomatic arch cranial to the external ear. The pterygopalatine nerve then branches into the greater palatine, lesser palatine, and caudal nasal nerves. The greater palatine and lesser palatine nerves innervate the mucosa of the hard palate and floor of

the nasal vestibule, and the soft palate, respectively. The caudal nasal nerve innervates the nasal mucosa around the ventral meatus of the nasal cavity, maxillary sinus, and palate. The infraorbital nerve branches into the caudal, middle, and rostral superior alveolar branches innervating all of the maxillary teeth, the external and internal nasal branches, and the superior labial branches, innervating the most rostral labial and nasal surfaces of the nose and muzzle.[33,36,38]

The zygomaticotemporal nerve contains postganglionic parasympathetic fibers of the facial nerve (from the pterygopalatine ganglion) that supply the lacrimal gland. The lesser palatine nerve also contains postganglionic parasympathetic fibers (from the geniculate ganglion) that supply visceral afferent fibers to the soft palate as well as taste fibers, and the caudal nasal nerve contains postganglionic parasympathetic fibers (from the pterygopalatine ganglion) that supply the nasal and palatine glands. The greater palatine nerve also contains parasympathetic fibers supplying the palatine glands.[36,37]

The mandibular nerve (V3)

The mandibular nerve exits through the oval foramen, separating into many branches providing both motor and sensory innervation to the buccal cavity, tongue, lower teeth, lower lip, skin of portions the head, cheek, commissure of the mouth, ear, and mucosa of intraosseous parts of the external ear. The branches providing motor innervation to the muscles of mastication and are the masticator, masseteric, deep temporal, and lateral and medial pterygoid nerves, innervating the masseter, temporalis, and lateral and medial pterygoid muscles. The tensor tympani nerve provides motor innervation to the tensor tympani muscle of the malleus and the tensor veli palatini nerve provides motor to the thin muscle of the soft palate. The remaining mandibular nerve

branches provide only sensory innervation to their respective areas of the face. The buccal nerve innervates the tissues of the cheek. The auriculotemporal nerve innervates the mandible, skin of the temporal region and external ear, and lining of the canal leading to the tympanum. The transverse facial nerve innervates the skin at the commissure of the lips. The lingual and sublingual nerves innervate the tongue and floor of the oral cavity. The inferior alveolar, mylohyoid, and mental nerves innervate the mandibular teeth, the mylohyoid muscle, and the lower lip and chin, respectively. The branches of the mandibular nerve do not provide any innervation to the nasal cavity or structures of the nose.[36-38,40]

The auriculotemporal and buccal nerves contains postganglionic parasympathetic branches of the glossopharyngeal nerve (from the otic ganglion) innervating the parotid salivary glands and buccal glands, respectively. The lingual nerve branches to the superficial sublingual nerve that joins visceral efferent fibers of the facial nerve (from the mandibular ganglion) to innervate the salivary glands, and gustatory fibers of taste buds (from the geniculate ganglion of the facial nerve) of the rostral two-thirds of the tongue.[37,38]

Regional anesthetic techniques

Regional nerve blocks have been performed for years, especially to provide anesthesia for dental, mouth, and ocular procedures in human and animal patients.[41-44] In human patients, a greater emphasis has been on the use of regional anesthesia for many areas of the face, including the eye, nose, and mouth, in order to complete painful procedures without the need for general anesthesia and the associated risks.[45] In our animal patients, the use of regional nerve blocks can decrease the nociception, resulting

in the use of a lighter plane of anesthesia, more stable vital signs, smoother recoveries, and earlier discharge from the hospital.[46] Similar results were also seen with the use of regional nerve blocks in human pediatric patients for maxillofacial surgeries, decreasing the post-operative need for analgesics and respiratory complications,[47] as well as decreased post-operative stress response.[48] Providing pre-emptive analgesia,[49] especially the use of local anesthetics in the form of regional nerve blocks, prior to inducing pain associated with surgical trauma, is one of the modalities commonly sought for multimodal anesthesia.

Maxillary nerve block studies

Blocking portions of the trigeminal nerve has been used for years to provide local anesthesia for dental procedures in dogs, though Cremer et al.[50] recently questioned if blocking the maxillary and infraorbital nerve would be successful for nasal procedures such as rhinoscopy in the dog. A percutaneous approach to the maxillary nerve[51] and an infraorbital nerve block using lidocaine was evaluated for anterior and posterior rhinoscopy using a flexible endoscope. The results showed that the maxillary block decreased the incidence of adverse reactions during posterior rhinoscopy, with more stable cardiovascular parameters compared to the infraorbital block or a sham block.[50]

Viscasillas et. al. published a novel method to approach the maxillary nerve to provide a safer technique for inexperienced anesthetists to block the maxillary nerve with a greater success rate with staining of nerves, without increasing the incidence of complications than the percutaneous technique. Providing anesthesia to the maxillary nerve in the pterygopalatine fossa can block a portion of the sensory innervation from the nasal cavity and provide patients with a safer anesthetic episode as well as several hours

of postoperative analgesia. In this cadaver study, it was found that complete staining of the maxillary nerve via the infraorbital approach was greater than that seen via the percutaneous approach, when performed by inexperienced anesthetists. The use of an intravenous over-the-needle catheter may decrease the incidence of trauma to the nerves or vasculature in the area of the infraorbital canal and pterygopalatine fossa. Though there was no gross trauma to the vasculature or intravascular injection, this was evaluated in cadaver dogs, making it difficult to compare to live dogs.[52]

A third method to anesthetize the maxillary nerve was studied by Langton et al. using a transorbital approach to the maxillary nerve in the pterygopalatine fossa. This was compared to the traditional percutaneous approach to the maxillary nerve, determining that in cadaver dogs, there was a greater staining success rate with the transorbital approach than the traditional percutaneous approach, both performed by the same inexperienced anesthetists.[53] Potential complications that could result from this technique are trauma to the eye, increasing intraocular pressures, and a potentially fatal oculocardiac reflex.[54,55] This is a sudden vagal-induced bradycardia associated with traction to the extraocular muscles or pressure on the globe. This occurs via the long and short ciliary and ophthalmic nerves, through communication between the ciliary and trigeminal ganglia, and the vagus nerve, with cardio-inhibitory fibers terminating in the myocardium. The vagal stimuli result in negative inotropic and chronotropic effects on the heart, manifesting as a sudden bradycardia.[56] This reflex is abolished and resolves with discontinued manipulation of the globe and anticholinergic therapy.[57]

Attempts can also be made to block the ophthalmic branch of the trigeminal nerve, as is performed in human patients undergoing trigeminal ganglion blockade for

trigeminal neuralgia or other pain syndromes,[35,44,58] and blocking the ethmoidal, nasociliary, and infratrochlear nerves for outpatient nasal surgery.[59] The anatomy of the human skull allows for direct access to the trigeminal ganglion,[44] which may be more difficult in the canine patient population, with varying skull shapes.[36] This procedure also does not go without risk, as the trigeminal ganglion is within the skull, immediately adjacent to the brainstem.[35,37]

The ophthalmic nerve alone cannot be blocked using any local anesthetic technique. The ophthalmic nerve exits the skull within the periorbita, along with the optic nerve and vasculature to the globe.[37] To get regional anesthesia of the ophthalmic nerve branches, a block technique penetrating into or adjacent to the orbital cone must be performed, such as a retrobulbar, peribulbar, or Peterson block.[60-62] Each of these techniques have been associated with complications such as hemorrhage, puncture of the globe, and trauma to the optic nerve.

With the information from these previous studies, the use of the infraorbital approach to apply local anesthetics to the maxillary nerve and its branches may be of benefit to patients undergoing rhinoscopy with nasal biopsy. It is understood that the maxillary branch of the trigeminal nerve does not supply complete innervation to the nasal cavity, it may be successful at blocking a portion of the nerve, while employing a technique that can be successfully performed by inexperienced anesthetists without additional complications.

Local anesthetics

Since the mid 1800's, local anesthetics have been used, specifically cocaine, to desensitize areas of the body, making the patient unaware of the painful medical

procedure being undertaken, and remaining unaware for several hours afterward while in recovery. Cocaine was determined to be addictive and hallucinogenic, and great strides were made to develop different compounds that are less toxic, yet provide the same local anesthetic properties as cocaine. The first versions of non-cocaine local anesthetics had a high potential for allergic reactions, and many different local anesthetics have been synthetized since then leading to the development of the local anesthetic compounds used today.[63]

Local anesthetics are a class of drugs that provides reversible motor and sensory blockade by blocking generation and propagation of nerve impulses. The movement of sodium into the cell through voltage-gated sodium channels is required for propagation of an action potential, local anesthetics impede nerve conduction and nerve cell membrane depolarization by blocking the influx of sodium ions through voltage-gated sodium channels, and to a lesser extent, by blocking voltage-dependent potassium and calcium channels.[63-65] Local anesthetics exhibit a pattern of sensory and motor blockade that can be seen clinically in patients, known as a 'differential block', causing first vasodilation, then loss of temperature and sharp pain sensation, then light touch, and finally motor blockade.[66] To achieve complete sensory blockade, the local anesthetic must reach three consecutive Nodes of Ranvier, known as the 'critical length' needed to disrupt nerve impulse propagation.[67,68] This requires that local anesthetics be injected into a specific location that the sensory blockade is to be achieved, making the knowledgeable use of local and regional anesthetic techniques of utmost importance.

The different local anesthetic agents used clinically are lipophilic molecules that contain a benzene ring and amide group that are bound with either an amide or ester

linkage, and their effectiveness is reliant upon its lipophilicity and degree of protein binding within the tissues. These properties alter the onset and duration of action of local anesthetics, making different local anesthetic agents appropriate for the duration of local anesthesia we aim to achieve. The most commonly used local anesthetic agents used in veterinary medicine are lidocaine, bupivacaine, and mepivacaine. Each agent has its own unique properties that make their use appropriate in various clinical situations.

Lidocaine

Lidocaine is a short-acting, amino-amide local anesthetic that is one of the most commonly used in both human and veterinary medicine. The rapid onset time and moderate toxicity makes lidocaine the most versatile local anesthetic used today. Duration of anesthesia of lidocaine alone as an infiltrative block is about 1 hour, though when combined with adjunct agents, its duration can be prolonged up to 3 hours or longer.[69] Lidocaine is also a Class Ib antiarrhythmic drug that can be given intravenously, working by shortening the action potential duration and refractory period in normal cardiac myocytes, and prevents ischemia-mediated shortening of ventricular depolarization in damaged myocytes, making its use for ventricular arrhythmias its most important pharmacologic activity.[70] Lidocaine can decrease the requirements for inhalant anesthetics needed as an intravenous component of multimodal anesthesia.[15,71]

Bupivacaine

Bupivacaine, a long-acting, amino-amide local anesthetic agent, commonly used in veterinary medicine, has an onset time of 20-30 minutes, and may provide desensitization for up to 10 hours following injection in the dog.[72] It can be used for local

infiltrative techniques only, as the drug is highly cardiotoxic, and intravenous injection can result in death. All local anesthetics have direct negative inotropic effects on the heart,[73] however, long-acting local anesthetics are more arrhythmogenic than shorter-acting drugs, due to the duration of time required for unbinding from cardiac sodium channels. In electrocardiographic and echocardiographic studies performed in the dog, bupivacaine caused a sudden impaired ventricular systolic function followed by profound right ventricular dilation following IV administration, with multiple ECG changes including widening of the QRS complex, bradycardia, ventricular arrhythmias, and electromechanical dissociation.[74] These changes are likely due to the effect on sodium and calcium channels, decreasing myocardial contractility.[75,76] These properties become exacerbated in the anesthetized animal, making the arrhythmogenic potential of bupivacaine even greater at high doses, or with high plasma concentrations seen following inadvertent intravenous administration.[63,64]

Even with the potential for significant cardiotoxicity in animal patients, bupivacaine provides the longest duration of desensitization of all of the clinically used local anesthetics today, and with careful use of bupivacaine given as an infiltrative injection at therapeutic doses, bupivacaine is a great choice for long-term local anesthesia in the dog.

Mepivacaine

Mepivacaine is another amino-amide local anesthetic that is pharmacologically similar to lidocaine with a longer duration of effect up to 2 hours. Its main use in veterinary medicine is for peripheral nerve blocks in horses, as it is the least neurotoxic of all commonly used local anesthetics.[77] Its use is not very common in small animal

medicine, as lidocaine and bupivacaine use has been more popular and more accepted for local anesthetic techniques, as neurotoxicity and ataxia are less concerning in our small animal patients.[64]

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CHAPTER II

EVALUATION OF A MODIFIED INFRAORBITAL APPROACH FOR A MAXILLARY NERVE BLOCK FOR RHINOSCOPY WITH NASAL BIOPSY OF DOGS

Introduction

Rhinoscopy with concurrent nasal biopsy is considered to be a core component for investigation of nasal disease of dogs.[1] To the authors' knowledge, there is not a simple and effective method that provides regional anesthesia to the nasal cavity for rhinoscopy and biopsy. Sudden periods of arousal during rhinoscopy and nasal biopsy are often observed clinically and can be associated with movements such as sneezing, head shaking, and chewing. These movements have potential to cause injury to patients and damage to expensive endoscopy equipment. To decrease the likelihood of movement, rhinoscopy patients are often maintained at a deep plane of anesthesia, which causes dose-dependent cardiorespiratory depression that can lead to hypotension and apnea.[2–5] Use of multimodal anesthesia, including local anesthetics for a local or regional nerve block, may help to decrease the amount of inhalation anesthetics required, thereby decreasing the severity of complications associated with a deep plane of anesthesia.[6–9]

Providing regional antinociception to the nasal cavity and corresponding structures is challenging because of the complexity of innervation to the face and nose. Knowledge of the anatomy of these nerves is needed to safely and effectively provide

regional antinociception. A comparison of percutaneous maxillary nerve blocks and infraorbital nerve blocks in dogs undergoing rhinoscopy revealed that the maxillary nerve block was superior to the infraorbital block for preventing adverse reactions during rhinoscopy of the caudal portion of the nasopharynx.[10] However, some authors believe that the infraorbital approach is more successful than the percutaneous approach for maxillary nerve blocks when performed by inexperienced anesthetists[11] and that the percutaneous approach is more difficult to perform because of its anatomic location.[10] Modifying an infraorbital approach to the maxillary nerve, similar to the procedure performed in canine cadavers,[11] could offer an alternative, simple method for approaching the maxillary nerve with a higher rate of success than for the traditional percutaneous approach.

The trigeminal nerve and its branches provide innervation (motor, sensory, and autonomic) to the face and nose and course through the pterygopalatine fossa. The maxillary branch of the trigeminal nerve provides sensory innervation to the nose, mucosa of the hard and soft palates, nasal vestibule, and choana via the pterygopalatine, greater palatine, lesser palatine, and caudal nasal nerves, respectively.[12,13] The ophthalmic branch of the trigeminal nerve innervates most of the internal structures of the nose, including the nasal turbinates, septum and lateral walls of the nasal cavity, and portions of the nasal mucosa, and external structures of the eyes.[14,15] The ophthalmic nerve of dogs is in an anatomic location that is difficult and dangerous to approach; thus, a simple approach that provides access to the maxillary nerve branches (which would partially desensitize the nasal cavity) is necessary to provide antinociception for nasal procedures such as rhinoscopy and biopsy.

The objectives of the study reported here were to investigate the feasibility of a modified infraorbital approach for a maxillary nerve block during a preliminary experiment with canine cadavers then to conduct an in vivo study to assess the effectiveness of the modified infraorbital approach for a maxillary nerve block in dogs undergoing rhinoscopy and nasal biopsy. We hypothesized that dogs administered local anesthetic in the pterygopalatine fossa via this maxillary nerve block technique would have better anesthetic outcomes, decreased procedural nociception, and smoother recovery (as indicated by better stability of vital parameters, decreased purposeful movement, decreased plasma concentrations of stress biomarkers, and lower pain scores during the recovery period), compared with results for a nonanesthetic control treatment.

Materials and Methods

Animals

Cadavers of 3 hound-type dogs were used in a preliminary experiment. Dogs were euthanized[a] for reasons unrelated to the present study at the conclusion of a teaching laboratory.

Eight healthy adult (age range, 1 to 2 years) purpose-bred hound-type dogs were used in an in vivo experiment. There were 4 spayed females, 3 sexually intact females, and 1 sexually intact male. Mean ± SD body weight was 21.7 ± 2.1 kg. The dogs were deemed healthy on the basis of results of physical examination, serum biochemical analysis, and a heartworm test and evaluation of platelet count, prothrombin time, activated partial thromboplastin time, PCV, and total solids concentrations. All dogs were American Society of Anesthesiologists physical status class I. The study was approved by

the Institutional Animal Care and Use Committee at the Mississippi State University College of Veterinary Medicine.

Cadaver experiment

An infraorbital approach to the maxillary nerve described in another study[11] was replicated in each canine cadaver. A slight modification in the procedure (adjustment of the distance the catheter was inserted through the infraorbital canal into the pterygopalatine fossa) was performed to determine the best method for a maxillary nerve block via the modified infraorbital approach to maximize delivery of local anesthetic to the maxillary nerve and its branches within the pterygopalatine fossa. A 1% solution of methylene blue stain[b] was injected into the pterygopalatine fossa; volume of injectate was 1, 1.5, and 3 mL as determined on the basis of published regional techniques that involved the use of 0.5% bupivacaine.[16] The stained and contralateral unstained pterygopalatine fossa were carefully dissected, and tissues were evaluated to detect trauma to the nerves or surrounding tissues as well as the degree of staining for each of the nerves.

In vivo experiment

Experimental design

A blinded, placebo-controlled, crossover study was performed. Each dog was randomly assigned (by a veterinary anesthesia technician who chose every other dog from a list) to receive 0.5% bupivacaine (0.5%, 0.1 mL/kg) or an equivalent volume of saline (0.9% NaCl) solution as a maxillary nerve block via the modified infraorbital

approach. After a 14-day washout period, each dog received the alternate treatment on the contralateral side.

The number of dogs in the study was determined by use of a power analysis. It was assumed 4 dogs would be randomly assigned to receive the bupivacaine treatment and the saline solution treatment in a crossover design whereby differences in mean changes from baseline values for the various outcomes would be assessed with a paired *t* test. Estimates of the variation anticipated for bupivacaine and saline solution treatments were based on published values for a similar study[10] that was conducted to compare responses of dogs with maxillary nerve blocks to those of control dogs. The SDs reported in that study[10] for control dogs for changes in heart rate (6 beats/min) and MAP (5 mm Hg) and for dogs with maxillary nerve blocks for changes in heart rate (6 beats/min) and MAP (4 mm Hg) were used in the power calculations for the study reported here. For α = 0.05, correlation between paired measures within a dog = 0.5, and a 1-tailed test, those SDs were used to estimate power of the study by use of available software.[17,c] The 8 pairs of samples would allow detection of a difference in heart rate of 6 beats/min (power, 0.82) and a difference in the change in MAP of 4.5 mm Hg (power, 0.80).

Anesthesia

Food, but not water, was withheld for 12 hours before induction of anesthesia. Dogs were premedicated with acepromazine maleate[d] (0.01 mg/kg, IM) and hydromorphone[e] (0.1 mg/kg, IM). Twenty minutes after administration of the premedication, an 18-gauge, 5-cm catheter[f] was placed in a cephalic vein. Anesthesia was induced with propofol[g] (2 to 4 mg/kg, IV, to effect), dogs were endotracheally intubated, and anesthesia was maintained with isoflurane[h] (calibrated vaporizer[i] setting of 1.5 vol%)

in oxygen (1.5 L/min) by use of a partial rebreathing circuit to achieve a surgical plane of anesthesia, as evaluated by jaw tone, palpebral reflex, and eye position. Dogs were mechanically ventilated[j] to maintain end-tidal partial pressure of CO_2 of 35 to 45 mm Hg. Vital parameters were monitored by use of a multiparametric monitor[k] and gas analyzer.[l] Oscillometric blood pressures were monitored by use of an appropriately sized cuff on a forelimb. A 20-gauge, 3.2-cm catheter[f] was placed in a dorsal pedal artery or an 18-gauge, 5-cm catheter[f] was placed in a lateral saphenous vein; catheters were used for collection of blood samples that were assayed to determine plasma cortisol and norepinephrine concentrations. A forced-air warming device[m] was used to maintain body temperature between 37.2° and 38.3°C. Lactated Ringer's solution[n] was administered (5 mL/kg/h, IV). Heart rate, SAP, MAP, and DAP were manually recorded by the same 2 investigators (KMF and L-HK) every 5 minutes during anesthesia as well as before the start of rhinoscopy (baseline), at the time of retroflexion of the endoscope in the caudal portion of the nasopharynx, at the time of nasal biopsy, 5 minutes after biopsy, and 10 minutes after biopsy. Atropine[o] (0.02 mg/kg, IV) was administered as needed to resolve substantial bradycardia associated with hypotension (MAP < 60 mm Hg). Dogs that had purposeful movement (paddling, head shaking, chewing, or licking) that interfered with procedures received additional propofol (0.5 mg/kg, IV).

Maxillary nerve block via a modified infraorbital approach

The location of the infraorbital canal was determined as a small indentation dorsal to the third premolar that was palpable through the oral mucosa. A 20-gauge, 5-cm over-the-needle catheter[f] was placed in the infraorbital canal parallel to the maxilla and directed caudally **(Figure 2.1)**. The catheter was inserted to a depth of 5 mm, after which

the cannula was withdrawn until the end was just within the tip of the catheter. The catheter and cannula then were advanced until the hub of the catheter touched the gingiva or resistance was encountered, whichever came first. Once the catheter was securely within the infraorbital canal, the cannula was removed. Either 0.5% bupivacaine[e] (0.5 mg/kg [0.1 mL/kg]) or an equivalent volume of saline solution[p] was placed in a 3-mL-syringe[q] and injected into the infraorbital canals. The syringe was attached to the catheter, aspiration was performed, and if no blood was aspirated, the solution was slowly injected. If there was resistance to injection, the catheter was repositioned 2 to 3 mm to ensure it was not within the perineurium or another vital structure,[18,19] aspiration was performed, and if no blood was aspirated, the volume was slowly injected. All regional nerve blocks were performed by the same investigator (KMF).

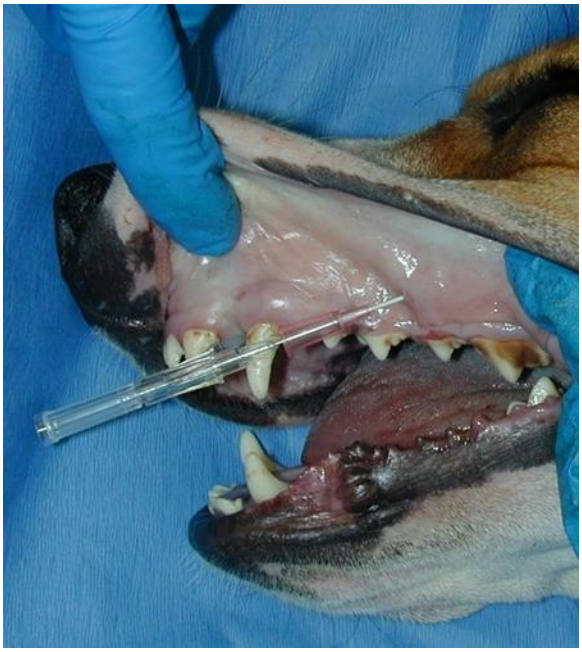

Figure 2.1 Maxillary nerve block technique

Photograph of a canine cadaver that illustrates a modified infraorbital approach for a maxillary nerve block. The location of the infraorbital canal was determined as a small indentation dorsal to the third premolar that was palpable through the oral mucosa. A 20-gauge, 5-cm over-the-needle catheter was placed in the infraorbital canal parallel to the maxilla and directed caudally. The catheter was inserted to a depth of 5 mm, after which the cannula was withdrawn until the end was just within the tip of the catheter. The catheter and cannula then were advanced until the hub of the catheter touched the gingiva or resistance was encountered, whichever came first.

Rhinoscopy and biopsy

Dogs were allowed to remain undisturbed in sternal recumbency for 30 minutes after the maxillary nerve block to enable the local anesthetic to take effect.[20] Standard rhinoscopy with nasal mucosal biopsy then was performed on the left side of the nose. An initial evaluation of the caudal portion of the nasopharynx was performed by retroflexion with a standard pediatric gastroscope.[r] Direct examination of the nasal mucosa and turbinates then was performed by use of a rigid endoscope[s] passed through the rostral aspect of the nares. A single pinch biopsy specimen of tissues of the nasal cavity was blindly obtained from the left side of the nose by use of an 8-mm biopsy instrument,[t]

placed in neutral-buffered 10% formalin,[u] and submitted for histologic examination. All rhinoscopy and biopsy procedures were performed by the same investigator (TMA). Dogs remained anesthetized until postbiopsy blood samples were obtained and bleeding from the biopsy site was controlled. After each dog had a 14-day washout period, the procedures were repeated on the right side of the nose but with injection of the alternate treatment solution for the maxillary nerve block.

Anesthetic recovery and postoperative pain scores

All dogs recovered from anesthesia in the intensive care unit. Vital parameters (heart rate, respiratory rate, and rectal temperature) were monitored until dogs were extubated and able to maintain sternal recumbency. Postoperative pain scores were obtained by use of the Glasgow Composite Pain Scale–Short Form[21] (scale, 0 to 24), a VAS[v] with a 10-cm scale, and the Colorado State University Canine Acute Pain Scale[22] (scale, 0 to 4). Pain scores and vital parameters were recorded after extubation and 1, 2, 3, and 4 hours thereafter. Hydromorphone[e] (0.1 mg/kg, IV) was used for postoperative rescue analgesia if dogs had a score > 6 of 20 or 8 of 24 for the Glasgow Composite Pain Scale–Short Form, ≥ 3 cm for the VAS, or ≥ 3 for the Colorado State University Canine Acute Pain Scale. All postoperative pain scores were assigned by 2 investigators (KMF or BET).

Collection of blood samples

A blood sample (3 mL) was collected before the start of rhinoscopy (baseline), at the time of retroflexion of the endoscope in the caudal portion of the nasopharynx, at the time of biopsy, 5 minutes after biopsy, and 10 minutes after biopsy. Blood samples (10

arterial and 6 venous) were placed in EDTA blood collection tubes.[w] Plasma was harvested, and 500 µL of plasma was mixed with 25 µL of 70% perchloric acid[x] and frozen at –80°C until analyzed to determine cortisol and norepinephrine concentrations.

Cortisol analysis

Frozen plasma samples were allowed to thaw at room temperature (20°C). Atrazine mercapturate[x] was added as an internal standard (final concentration, 1µM). Samples were mixed on a vortex device, placed on ice, and then centrifuged (1,300 X *g* at 4°C for 15 minutes) to remove protein precipitate. Supernatant was transferred to high-performance liquid chromatography vials. Samples were analyzed for cortisol by use of liquid chromatography–mass spectrometry[y,z] as described elsewhere.[23] A stock solution of cortisol (5µM) was prepared in methanol[x] and used to create calibration standards in PBS solution. Concentration of calibration standards ranged from 0.1nM to 100nM. New calibration standards were prepared for each set of unknown samples. Each calibration curve yielded comparable results ($r^2 > 0.990$). The limit of quantification for cortisol was estimated as 0.25nM.[23]

Norepinephrine analysis

Frozen plasma samples were allowed to thaw at room temperature (20°C). A 1M tris solution containing 25 ng of 3,4-dihydroxybenzylamine[x] was added as an internal control. Samples were centrifuged (1,300 X *g* at 4°C for 20 minutes) and then centrifugation was repeated without disruption of the pellet. The supernatant was transferred to microtubes containing 5 g of aluminum oxide[x] and 500 µL of the tris–3,4-dihydroxybenzylamine solution. Samples were shaken for 30 minutes and then

centrifuged (1,300 X *g* for 30 seconds), and the supernatant was discarded. The pellet was washed with 500 µL of reverse-osmosis water and then centrifuged (1,300 X *g* for 30 seconds), and the supernatant was discarded. Washing was repeated, after which the pellet was retrieved and 200 µL of 100mM citric acid[x] was added. The sample was shaken for 15 minutes and then centrifuged (1,300 X *g* for 30 seconds), and the supernatant was harvested and analyzed. Supernatants were injected into a high-performance liquid chromatography system with an electrochemical detector[aa–cc] by use of a mobile phase of 100mM phosphate,[x] 17.5% methanol,[x] 25µM EDTA,[x] and 1mM octyl sodium sulfate[x] (pH, 3.65). The quantity of each compound was determined by comparison with known concentrations in standards of norepinephrine.[x] Concentration of calibration standards ranged from 0.1 to 100 ng. New calibration standards were prepared for each set of unknown samples. Each calibration curve yielded comparable results (r^2 > 0.990). The limit of quantification was not evaluated because all data points were within limits of the calibration standard curve.

Histologic examination of nasal biopsy specimens

Formalin-fixed nasal biopsy specimens were routinely processed, embedded in paraffin, and sectioned at a thickness of 5 µm. Slides were stained with H&E stain for evaluation. All histologic changes were evaluated by the same investigator (AKO). The degree of lymphoplasmacytic inflammation was scored on a scale of 0 to 3 as follows: 0 = no inflammation, 1 = mild inflammation, 2 = moderate inflammation, and 3 = severe inflammation. At least four 20X fields were evaluated for each specimen.

Statistical analysis

Separate linear mixed models[dd] were fit for heart rate, SAP, MAP, DAP, plasma cortisol concentration, plasma norepinephrine concentration, and the Glasgow Composite Pain Scale–Short Form score. First or second anesthetic event (run), order of treatment (sequence), treatment, time point, histologic score, treatment-by-time point interaction, and treatment-by-histologic score interaction were included as fixed effects with a Kenward-Rogers degrees of freedom method. Baseline measurement was also included in the model as a covariate to adjust for variation in the result among dogs prior to the start of rhinoscopy; consequently, time point included retroflexion, biopsy, 5 minutes after biopsy, and 10 minutes after biopsy. Dog was included as random effect with a variance component covariance structure. Repeated measures of dog within run for the various time points were specified in a repeated statement with an autoregressive 1-covariance structure. When sequence or run were not significant, they were sequentially removed from the model. Treatment-by-histologic score interaction, histologic score, or treatment-by-time point interaction were also removed when they were not significant. Treatment and time point were the variables of greatest interest and remained in the model regardless of significance. Differences in least square means were determined for outcomes with significant effects. The *P* values were adjusted to account for multiple comparisons by use of a simulation option,[ee] which was used to estimate the critical value while incorporating the correlation structure of the model and can be an effective method for multiple comparisons for mixed models.[24] In the case of a significant effect for the treatment-by-time point interaction, differences in least square means between treatments were determined at each time point and among time points within each treatment by use

of estimation statement[ff] with a simulation adjustment for multiple comparisons. Distribution of the conditional residuals was evaluated for each outcome to ensure assumptions of the statistical model had been met.

Purposeful movement and Colorado State University Canine Acute Pain Scale scores were dichotomized (absent or present); VAS also was dichotomized (absent was ≤ 1 cm and present was > 1 cm). After dichotomization was performed, logistic regression by use of a separate generalized linear mixed model[gg] was fit for purposeful movement, Colorado State University Canine Acute Pain Scale scores, and VAS. Run, sequence, histologic score, and treatment were included as fixed effects. Dog was included as a random effect with a variance component covariance structure. When sequence or run were not significant, they were sequentially removed from the model. Histologic score was also removed if not significant. Values of $P < 0.05$ were considered significant. All data are described as mean ± SEM.

Statistical analysis of histologic results were evaluated by use of the Mann-Whitney *U* test. One dog was excluded from the histologic analysis because it was considered an outlier that would have skewed the results. Values of $P < 0.05$ were considered significant.

Results

Cadaver experiment

Results of the cadaver experiment indicated that for use of a modified infraorbital approach to the maxillary nerve block, 3 mL of methylene blue was required to stain all branches of the maxillary nerve within the pterygopalatine fossa, including the zygomatic, pterygopalatine, greater palatine, lesser palatine, caudal nasal, infraorbital,

and superior alveolar nerves **(Figure 2.2)**. Smaller volumes did not penetrate all of the nerves. A volume of 3 mL was equivalent to 0.5 mg of 0.5% bupivacaine/kg (0.1 mL/kg) injected into each pterygopalatine fossa. Gross trauma to the nerves or surrounding structures within the infraorbital canal or pterygopalatine fossa was not detected. All nerves had > 6 mm of staining, which indicated that a complete nerve block would have resulted from the use of a 3-mL volume of local anesthetic[25–27]; thus approximately 3 mL of injectate was used for the in vivo experiment (adjusted to a volume of 0.1 mL/kg for each nerve block).

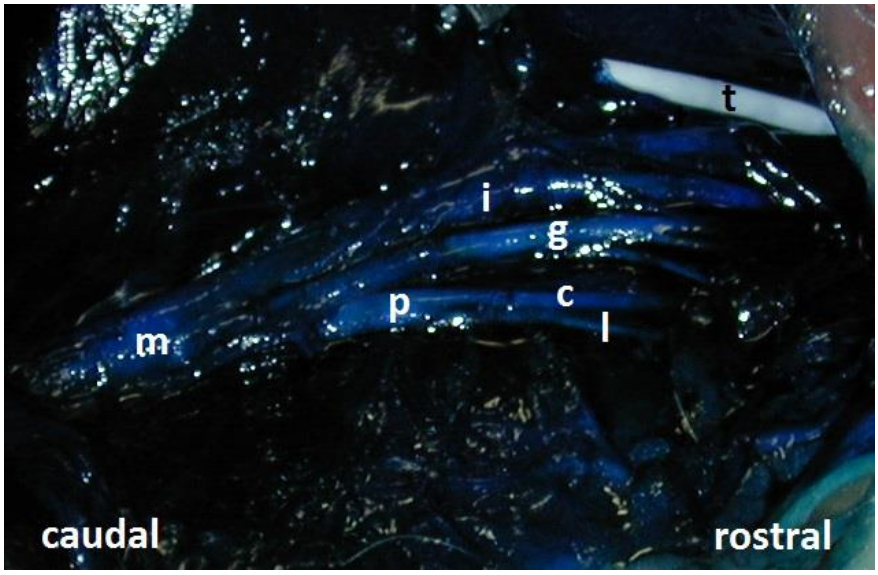

Figure 2.2 Nerve staining

Photograph of structures in the right pterygopalatine fossa following injection of 3 mL of methylene blue via a 20-gauge, 5-cm catheter placed into the pterygopalatine fossa through the infraorbital canal by use of a modified infraorbital approach for a maxillary nerve block. There is complete staining of the maxillary nerve and its branches. Notice the maxillary nerve (m), infraorbital nerve (i), greater palatine nerve (g), pterygopalatine nerve (p), caudal nasal nerve (c), lesser palatine nerve (l), and tip of the catheter (t).

In vivo experiment

Fixed effects of sequence, run, histologic score, treatment-by-histologic score interaction, and treatment-by-time point interaction were not significant and removed from the models for SAP, MAP, DAP, heart rate, and norepinephrine concentration; treatment and time point remained in the models as fixed effects regardless of significance. The baseline value for each outcome was included in the models regardless of significance to act as a covariate to control for differences in baselines values among dogs.

Compared with results for saline solution, bupivacaine had a significant effect on blood pressures when model was adjusted across all time points from retroflexion to 10 minutes after biopsy for baseline values **(Figure 2.3)**. Bupivacaine and saline solution differed significantly with regard to mean ± SEM for SAP (103 ± 2 mm Hg and 117 ± 3 mm Hg, respectively [$P = 0.005$]), MAP (74 ± 2 mm Hg and 93 ± 4 mm Hg, respectively [$P = 0.019$]), and DAP (59 ± 2 mm Hg and 81 ± 4 mm Hg, respectively [$P = 0.024$]). There was no significant effect of time point on SAP ($P = 0.864$), MAP ($P = 0.542$), or DAP ($P = 0.788$). Baseline values for each outcome were significant (all $P < 0.014$) in their respective models, which indicated there was variation among dogs prior to the start of rhinoscopy for each outcome. Including the baseline values in the model accounted for this source of variation.

Treatment did not have a significant ($P = 0.056$) effect on heart rate; however, there was a significant ($P < 0.001$) effect of time point on heart rate, when adjusted for the effect of treatment and baseline values (Figure 3). Mean ± SEM heart rate was significantly higher at biopsy (94 ± 5 beats/min) than at retroflexion (81 ± 5 beats/min [P

< 0.001]), 5 minutes after biopsy (84 ± 4 beats/min [$P < 0.001$]), and 10 minutes after biopsy (84 ± 4 beats/min [$P = 0.013$]). Three dogs (1 saline solution and 3 bupivacaine) received atropine, though there were no significant differences in heart rate between the dogs receiving atropine and untreated dogs. Significant ($P < 0.001$) variation in baseline heart rate among the dogs before the start of rhinoscopy was accounted for by inclusion in the model.

The treatment-by-time point interaction had a significant ($P = 0.038$) effect on plasma cortisol concentration **(Figure 2.4)**. Mean ± SEM plasma cortisol concentration increased significantly ($P = 0.006$) from biopsy (8.3 ± 1.6nM) to 5 minutes after biopsy (17.8 ± 4.7nM) for the saline solution treatment. There was a similar, but not significant ($P = 0.055$), increase between biopsy and 10 minutes after biopsy (17.8 ± 5.4nM) for the saline solution treatment. No other significant differences were detected among time points within the saline solution treatment (all $P > 0.157$), among time points within the bupivacaine treatment (all $P > 0.997$), or between bupivacaine and saline solution at any time point (all $P > 0.212$). Plasma norepinephrine concentrations did not differ significantly between bupivacaine and saline solution ($P = 0.212$) or among time points ($P = 0.783$).

In regard to clinical evaluation of dogs during rhinoscopy and nasal biopsy, 4 of 8 dogs had purposeful movement at least once during the procedure when injected with saline solution, whereas only 2 of 8 dogs had purposeful movement when injected with bupivacaine, but these proportions did not differ significantly ($P = 1.00$). The Glasgow Composite Pain Scale–Short Form scores for all dogs ranged from 0 to 11; there was no significant ($P = 0.24$) difference between scores for the saline solution and bupivacaine

treatments. Seven of 8 dogs had a score ≥ 1 (range, 0 to 2) for the Colorado State University Canine Acute Pain Scale when receiving saline solution, whereas 5 of 8 dogs had a score ≥ 1 (range, 0 to 2) when receiving bupivacaine; these proportions did not differ significantly ($P = 0.264$). Three of 8 dogs had a VAS score > 1 cm (range, 0 to 5 cm) when receiving saline solution, whereas 1 of 8 dogs had a VAS score > 1 cm (range, 0 to 5 cm); these proportions did not differ significantly ($P = 0.264$). One dog required postoperative analgesia immediately after extubation when receiving bupivacaine (Glasgow Composite Pain Scale–Short Form score, 11/24; VAS score, 5 cm). No other dogs in the study required postoperative analgesia.

Histologic examination of the nasal biopsy specimens revealed that all dogs had mild to severe lymphoplasmacytic inflammation in the lamina propria. Six dogs had the same inflammation score on both sides, 1 dog had a higher score for the side when saline solution was administered, and 1 dog had a chondrosarcoma for the side when saline solution was administered. There was not a significant ($P = 0.65$) difference in the degree of inflammation between the 2 treatments.

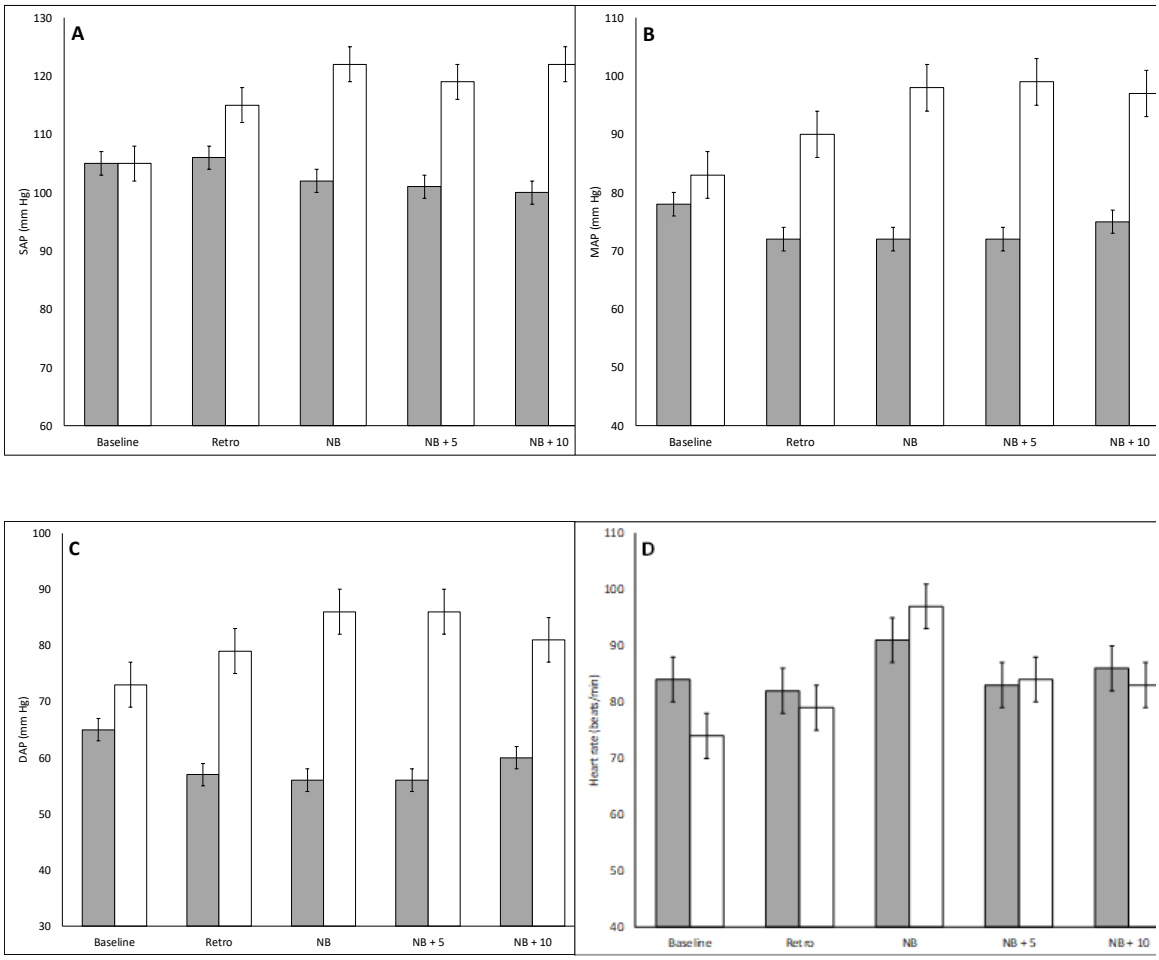

Figure 2.3 Blood pressure and heart rate

Mean ± SEM values for SAP (A), MAP (B), DAP (C), and heart rate (D) for 8 dogs that underwent rhinoscopy and nasal biopsy after receiving a maxillary nerve block via a modified infraorbital approach with 0.5% bupivacaine (gray bars) and an equivalent volume of saline (0.9% NaCl) solution (white bars). There was a 14-day washout period between treatments. Blood samples and recording of blood pressure and heart rate were performed immediately before start of rhinoscopy (Baseline), at the time of retroflexion of the endoscope in the caudal portion of the nasopharynx (Retro), at the time of nasal biopsy (NB), 5 minutes after nasal biopsy (NB + 5), and 10 minutes after nasal biopsy (NB + 10).

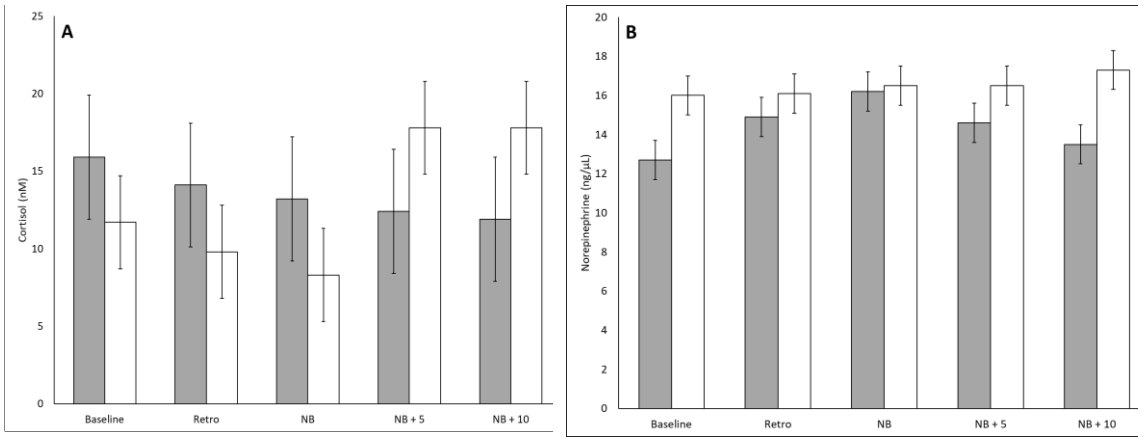

Figure 2.4 Cortisol and norepinephrine concentrations

Mean ± SEM values for plasma concentrations of cortisol (A) and norepinephrine (B) for 8 dogs that underwent rhinoscopy and nasal biopsy after receiving a maxillary nerve block via a modified infraorbital approach with 0.5% bupivacaine (gray bars) and an equivalent volume of saline (0.9% NaCl) solution (white bars). ***See*** Figure 3 for remainder of key.

Discussion

Use of the infraorbital canal to approach the maxillary nerve in the pterygopalatine fossa for administration of local anesthetic in healthy dogs undergoing rhinoscopy and nasal biopsy was associated with relatively limited changes, compared with results after the administration of saline solution. Significant differences between bupivacaine and saline solution were detected for several variables, including SAP, MAP, and DAP, when controlling for time point and baseline values in the model. Significant changes in plasma cortisol concentrations were detected when comparing biopsy versus 5 minutes after biopsy within the saline solution treatment. Similar, but not significant, changes were seen between biopsy versus 10 minutes after biopsy within the saline solution treatment. There was no significant difference between the treatments for heart rate, plasma norepinephrine concentration, purposeful movement, or postoperative pain

scores. There also was no subjective clinical difference between treatments during the anesthetic or recovery periods.

On the basis of the results of the present cadaver experiment and another cadaver study,[11] a maxillary nerve block via a modified infraorbital approach would be expected to block sensory transmission to all nerves within the pterygopalatine region that provide sensory innervation to structures of the nose and face. However, given the anatomy of these nerves in mesaticephalic dogs, a modified infraorbital approach to the maxillary nerve block cannot completely block sensation within the nasal cavity. Branches of nerves that travel through the nasal cavity are not in close proximity to the local anesthetic injected into the pterygopalatine fossa and are not subject to the effects of the local anesthetic. The ethmoidal nerve, a branch of the ophthalmic nerve that innervates portions of the nasal mucosa and turbinates,[13,14] courses along the orbital cone and not through the pterygopalatine fossa; therefore, it most likely cannot be blocked by use of a modified infraorbital approach. To block the ethmoidal nerve and provide desensitization to the nasal mucosa and turbinates, a different nerve block approach would be required, which was not investigated in the present study. The zygomatic nerve, a branch of the maxillary nerve that innervates portions of the tissue surrounding the eyes, could be blocked via a modified infraorbital approach, which would cause temporary desensitization to the superficial structures of the eyes and orbital cone but would not provide innervation to structures within the nasal cavity.[14]

In a recent study,[28] a transorbital approach to the maxillary nerve was evaluated and compared with a traditional percutaneous approach to the maxillary nerve. This transorbital approach, which is much more similar to maxillary nerve blocks performed

in humans, can also be difficult for inexperienced anesthetists and can be associated with additional complications. A modified infraorbital approach to the maxillary nerve can be performed by inexperienced anesthetists, without concerns about globe rupture, maxillary artery puncture, or oculocardiac reflex. Both approaches, with the addition of a modified infraorbital approach to the maxillary nerve block, can provide desensitization to portions of the nasal cavity, although a modified infraorbital approach may be easier for inexperienced anesthetists.

In humans, maxillary nerve blocks are used for facial and nasal procedures in sedated and anesthetized patients, to help minimize anesthetic complications, and to decrease postoperative pain. The maxillary nerve and its branches are easily approached in many nerve block methods in humans. Many of these nerve block methods are similar to those performed in dogs, but the anatomic orientation of the human nose and face differ from those of dogs. The close proximity of the maxillary and ophthalmic branches to each other in humans allows for local anesthetic to travel between these nerves, likely partially blocking the ophthalmic nerve when a maxillary or infraorbital nerve block is performed. Studies[29–32] in pediatric human patients have revealed a decreased opioid requirement and improved postoperative pain when comparing maxillary blocks with a placebo, and similar results have been seen in adult patients undergoing nasal procedures who received infraorbital nerve blocks.[33–36] In these same studies,[33-36] 1 to 3 mL of local anesthetic was administered to adults and 0.15 mL/kg was administered to pediatric patients, which are volumes comparable to those used in dogs in the study reported here. In the present study, a modified infraorbital approach to the maxillary nerve block was only tested in mesaticephalic hound-type dogs. Use of this nerve block technique in

brachycephalic dogs or in other species (eg, cats) with shorter trigeminal nerve branches has the potential to provide better antinociception. In those animals, a shorter distance for diffusion of the local anesthetic along the maxillary nerve to reach the ophthalmic nerve as well as a larger volume of local anesthetic relative to nerve length may result in a more complete blockade of the nasal mucosa and turbinates.

Blood pressures (SAP, MAP, and DAP) differed significantly between the treatments, with blood pressures generally higher during the study period for the saline solution treatment. Although heart rate increased more for the saline solution treatment than the bupivacaine treatment, this change was not significantly different between treatments. Blood pressures and heart rates typically were higher for the saline solution treatment than the bupivacaine treatment, which led us to suspect that dogs receiving the saline solution treatment had a greater nociceptive stimulus.[37] Some dogs (1 saline solution and 2 bupivacaine) were treated with atropine to resolve bradycardia associated with hypotension, which likely played a role in the blood pressure and heart rate changes, although atropine was administered prior to the start of the rhinoscopy and nasal biopsy procedures and before blood samples were collected or variables were recorded.

Cortisol and norepinephrine are biomarkers of stress and can be indicators of pain in humans and other animals.[38–40] Measurement of these biomarkers can be used to indicate stress responses attributable to nociception during anesthetic procedures,[37,38,41] postoperative pain,[42] trauma,[43] medication administration,[40,44] and behavioral stresses.[39,45–47] Norepinephrine is produced as an immediate response to stress,[39] whereas cortisol can take up to 4 to 6 hours to reach peak concentrations following surgical trauma.[43] However, changes in plasma norepinephrine concentrations were more

prolonged than changes in plasma cortisol concentrations in some studies.[37,44] The magnitude of change of plasma norepinephrine concentration following a nociceptive stimulus has been reported as being much smaller than that of the plasma cortisol concentration.[40] Variability in biomarker changes in response to a stimulus can make it difficult to interpret changes in plasma norepinephrine concentrations. In the present study, plasma cortisol and norepinephrine concentrations were measured before, during, and after rhinoscopy and nasal biopsy, and we found that plasma cortisol concentrations in dogs receiving saline solution increased significantly from biopsy to 5 minutes after biopsy, which suggested that the local anesthetic blocked nociceptive stimulation of the nasal cavity to some degree.[48] In contrast, no significant changes were seen in plasma norepinephrine concentrations at any of the measured time points. A longer postprocedure time period for measurement of plasma cortisol and norepinephrine concentrations may have provided more information regarding nociception, and stress in these dogs.

The dogs used in the present study were a subjectively normal, healthy group that consisted of a sexually intact male and both sexually intact and spayed females. Sex and reproductive status did not factor into results for the study reported here because each dog served as its own control animal. Although including only dogs of the same sex and reproductive status would have provided a more uniform study population, this was not a viable option because of the dogs available for use at the time of the study.

On the basis of histologic examination of the nasal biopsy specimens, lymphoplasmacytic inflammation was seen in some dogs, but there was no difference between the 2 treatments with regard to severity of inflammation. An incidental

chondrosarcoma was found on 1 side of 1 dog receiving saline solution. No clinical evidence of disease was noted prior to obtaining biopsy specimens in any of the dogs in this study.

A modified infraorbital approach to the maxillary nerve block in the present study did not clearly reduce the degree of purposeful movement seen clinically during rhinoscopy and nasal biopsy, compared with results for the saline solution treatment. No subjective differences were seen during recovery between dogs when receiving saline solution or bupivacaine because pain scores were not significantly different between treatments at any time point. All pain scores were assigned by 2 investigators who were well versed on pain scoring rubrics prior to the start of the present study. One limitation of the study, especially for postoperative pain scoring, was that the subjects were relatively poorly socialized research dogs that had unpredictable behavior when placed in a cage within the intensive care facility and that were not conditioned to touching of their head and face.[46,47] Therefore, a portion of the similarities and differences in pain scores between dogs for the 2 treatments could have been based on behavior and not necessarily on pain. A future study in client-owned animals that are better conditioned to human interaction may change the outcome for postoperative pain scoring, which would potentially allow for behavioral changes attributable to pain to be differentiated from changes attributable to anxiety in a stressful environment.

Results of a power analysis performed before the start of the present study suggested that significant changes in heart rate and blood pressure would be detected when a small sample size (n = 16) was used. Had the study population been larger, additional significant differences, especially in heart rate, plasma norepinephrine

concentration, and pain score, may have been detected. Both cost and dog availability prohibited a larger study population, although a larger clinical study involving client-owned animals with clinically relevant nasal disease may provide additional significant findings.

On the basis of findings for the present study, there is evidence, including blood pressures and plasma cortisol concentration, that use of a modified infraorbital approach for a maxillary nerve block could decrease nociceptive and stress responses in dogs undergoing rhinoscopy and nasal biopsy. However, clinical implications for performing a maxillary nerve block via a modified infraorbital approach are not yet clear. There were no observed differences in purposeful movement, postoperative pain scores, or anesthetic recovery; thus, results of the present study suggested that the use of this nerve block technique may not cause any clinical differences in overt indicators of nociceptive responses in dogs. This nerve block technique was not studied in a variety of breeds of dog or in other species and was only investigated in healthy dogs that did not have outward clinical signs of nasal disease. A weakness of the study was that we did not test the modified infraorbital approach for a maxillary nerve block for efficacy in dogs without subsequent rhinoscopy and nasal biopsy, which could have ensured that the nerve block was able to block the appropriate nerves. It was possible that all dogs receiving bupivacaine did not have the same amount of pain control with the block. In patients with clinically relevant nasal disease, a modified infraorbital approach for a maxillary nerve block may cause different outcomes. In dogs that are not healthy, particularly those with systemic disease, dose-dependent cardiorespiratory effects of anesthetics are likely to be more profound, and this nerve block may help minimize these anesthetic complications in

dogs for which rhinoscopy and nasal biopsy are clinically indicated. Care should be used when performing this maxillary nerve block in dogs with a space-occupying lesion that spreads beyond the nasal cavity because potential seeding of tumor cells could result.[49,50]

In the study reported here, maxillary nerve block via a modified infraorbital approach resulted in evidence of decreased nociception, as determined on the basis of blood pressures and plasma cortisol concentrations associated with rhinoscopy and nasal biopsy; therefore, this maxillary nerve block technique could help reduce cardiorespiratory effects of inhalation anesthetics during nasal procedures. However, the lack of clinical differences in purposeful movements during nasal procedures and in pain scores during the recovery period suggested that this maxillary nerve block technique may not be effective in decreasing nociception during procedures and pain during the recovery period. Further investigation of a modified infraorbital approach for a maxillary nerve block in animals with clinically relevant nasal disease undergoing rhinoscopy and nasal biopsy are indicated.

Footnotes

a. VetOne Euthanasia, MWI, Boise, Idaho

b. Methylene blue 1%, Akorn Inc, Lake Forest, Ill.

c. G*Power 3.1.9.22, Heinrich-Heine-Universität, Düsseldorf, Germany, http://www.gpower.hhu.de/en.html.

d. Henry Schein Animal Health, Dublin, Ohio.

e. Hospira Animal Health, Lake Forest, Ill.

f. Surflo IV catheters, Terumo Medical Corp, Elkton, Md.

g. Abbott Laboratories, North Chicago, Ill.

h. Piramal Healthcare, Bethlehem, Pa.

i. Isotec vaporizer, Smiths Medical PM Inc, Norwell, Mass.

j. Hallowell ventilator, model 2002, Hallowell EMC, Pittsfield, Mass.

k. Vetrends V, Systemvet, Tampa, Fla.

l. Poet gas analyzer, Criticare Systems Inc, Waukesha, Wis.

m. 3M Bair Hugger, Arizant Inc, Eden Prairie, Minn.

n. Baxter Healthcare Corp, Deerfield, Ill.

o. MWI, Boise, Idaho.

p. B. Braun Medical Inc, Irvine, Calif.

q. Terumo syringe, Terumo Medical Corporation, Somerset, NJ.

r. Olympus GIF-XP160, Olympus America, Center Valley, Pa.

s. Storz E013, Karl Storz Endoscopy-America Inc, El Segundo, Calif.

t. Eppendorfer 9-inch biopsy forceps, MPM Medical Supply, Freehold, NJ.

u. Vedco Inc, St Joseph, Mo.

v. Visual Scales LLC, Encino, Calif.

w. Tyco Healthcare Group LP, Mansfield, Mass.

x. Sigma Aldrich, St Louis, Mo.

y. Thermo quantum access max, Thermo Fisher Scientific, San Jose, Calif.

z. Thermo Excaliber 2.0 software, Thermo Fisher Scientific, San Jose, Calif.

aa. Waters 2695 separation module, Waters Corp, Milford, Mass.

bb. SupleCosil LC-18-DB column, Waters Corp, Milford, Mass.

cc. Waters 2465 electrochemical detector, Waters Corp, Milford, Mass.

dd. PROC MIXED, SAS for Windows, version 9.4, SAS Institute Inc, Cary, NC.

ee. LSMEANS, SAS for Windows, version 9.4, SAS Institute Inc, Cary, NC.

ff. LSMESTIMATE, SAS for Windows, version 9.4, SAS Institute Inc, Cary, NC.

gg. PROC GLIMMIX, SAS for Windows, version 9.4, SAS Institute Inc, Cary, NC.

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CHAPTER III

CONCLUSION

Use of the modified infraorbital approach to the maxillary nerve in canine patients has been shown to have some effect in anesthetizing the structures of the nasal cavity in healthy dogs undergoing rhinoscopy with nasal biopsy. When comparing the dogs receiving bupivacaine to the dogs receiving saline, there was a significant decrease in blood pressures and plasma cortisol concentrations in the dogs receiving bupivacaine blocks. A complete nerve block of the nasal cavity was not achieved, though it appears that a partial nerve block was achieved, providing some benefit by decreasing nociception during the rhinoscopy and nasal biopsy procedure, as evidenced by a lower blood pressure and plasma cortisol concentration. Clinically, however, there did not appear to be any objective difference between the dogs receiving the block and dogs that did not, especially during the recovery period.

Pain score results were similar between the different treatments, though our evaluation and scoring methods may have been misleading. Our goal was to utilize three different pain scoring rubrics to help identify any differences in pain between the bupivacaine and saline treated dogs during the post-operative period, though that was not evident in this study. All of the dogs received similar pain scores, with only one dog in the bupivacaine treatment scoring high enough to warrant rescue analgesia. It was very difficult to determine if this dog was truly painful or instead responding to human

interaction and manipulation of the head and face. Being purpose-bred research dogs, they were not preconditioned to having their faces palpated and wearing an Elizabethan collar. During the recovery period, all of the dogs were hyper-responsive to anyone touching or being near their face, likely masking a true pain response with underlying anxiety. In this study, however, the response to manipulation of the face (response to palpation and Elizabethan collar placement) was not evaluated prior to anesthesia, making differentiating pain from stress and anxiety difficult. The dogs chosen for this study were from a research colony and were not well socialized to human interaction, at least to a level comparable to most companion dogs. Studies addressing behaviors in laboratory beagles showed that dogs bred within the facility are better socialized than dogs obtained from elsewhere, with striking differences in behavior and body language.[1] Though these dogs were quite well behaved, they did not possess the characteristics commonly seen in client-owned companion dogs, most notably behaviors associated with normal, everyday, human interaction.

Continuing this study protocol with clinical client-owned dogs may provide different results, especially with respect to pain scoring in the recovery period. With the significant differences seen in blood pressures and plasma cortisol concentrations, there is interest in the idea that dogs who are conditioned to human interaction, have been rewarded for social behavior, and regularly visit the veterinary hospital, may show very different pain scoring results than those seen by purpose-bred laboratory dogs. With regard to the pain scoring methods, it has been very difficult to develop a pain scoring system that is user friendly, does not have significant inter-observer differences, and can be validated in our animal patients.[2-4] Much like in human pediatric medicine, out

patients are unable to voice that they are experiencing pain, but will do so with subtle behavioral cues, with their level of training and social interaction affecting these cues.[1,5]

Differences in the anatomy of the dog nose, in comparison to that of the human face, can help to account for why this nerve block is not completely effective in anesthetizing all of the structures of the canine nose. Skull anatomy of the dog is significantly different than that of the human and proves anesthetizing the nose a difficult task. The orientation of the human skull is such that complete blockade of the trigeminal nerve can be accomplished, though this is not routinely used for diagnostic procedures and is reserved for use in severe pain disorders, such as trigeminal neuralgia.[6,7] Blockade of the trigeminal ganglion in the dog would be a risky procedure that could result in long term side effects, and accomplishing this may not be possible in the dog.

Altering the injectate used for the nerve block, such as by changing the drug combination or increasing the volume injected, may improve the benefit of this maxillary nerve block. By increasing the volume of local anesthetic injected, either by increasing the dose or diluting the same dose, a greater distance of spread of drug would occur and it may be more likely that some local anesthetic would reach the trigeminal ganglion or ophthalmic nerve. It also must be taken into account that local anesthetics are toxic at high doses and concentration does alter their analgesic effects. The addition of different drugs to the injectate, such as an opioid or α-2 agonist, may increase the duration of effect of the maxillary block, though not necessarily increase its spread to more distant nerves. Adjuncts are commonly used in conjunction with local anesthetics to improve analgesia effect and duration.[8]

Additional studies in clinically affected dogs may show more insight into the benefit of multimodal anesthesia in patients with disease processes that may complicate the effects of anesthesia. It is also difficult to presume, that in brachycephalic dogs and cats with significant facial anatomy variability, and shorter distance for the maxillary nerve to travel, that the modified infraorbital approach to the maxillary nerve can provide better anesthesia to the structures within the nasal cavity. The distance the local anesthetic needs to travel, as well as the volume of local anesthetic administered, may account for the incomplete block of the nasal cavity. Additional studies testing the differences between brachycephalic and mesaticephalic dog breeds, and cats, as well as testing different local anesthetics volumes may give greater insight into the clinical usage of this nerve block in veterinary patients undergoing rhinoscopy with nasal biopsy. The decreased blood pressure and plasma cortisol concentrations seen while under anesthesia gives us hope that testing this nerve block method in client owned animals, and in animals with increased anesthetic complication risks, may result in the outcome initially intended, with improvement in recovery scores and reduced anesthetic complications associated with rhinoscopy with nasal biopsy. Our hope is that this nerve block method can prove clinically beneficial, and a simple procedure for inexperienced anesthetists to perform. Regional nerve blocks, especially new approaches to classic procedures, can be very safe if performed correctly, and beneficial, providing long acting anesthesia and analgesia for animals undergoing various diagnostic and surgical procedures.

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