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Research Article

A Randomized Controlled Trial Comparing The Intrarectal And Intramuscular Impact Of A Combination Of Dexmedetomidine, Ketamine, And Midazolam On Cat Tear Production.

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Abstract

Cats are frequently uncooperative and easily agitated. In the feline species, sedatives are frequently employed for even simple clinical and diagnostic procedures. The objective of this research is to evaluate the effect of intrarectal (IR) injection of a combination of midazolam, ketamine, and dexmedetomidine as opposed to the intramuscular (IM) one. Twenty cats participated in a clinical trial that was blinded and randomized. The cats underwent an ophthalmological and clinical checkup. Dexmedetomidine 0.003 mg kg−1, ketamine 4 mg kg−1, and midazolam 0.4 mg kg−1 were given to the IR group; similarly, the IM group was given dexmedetomidine 0.003 mg kg−1, ketamine 2 mg kg−1, and midazolam 0.2 mg kg−1.One hour before to sedation, a Shirmer tear test I (STT-I) was performed, and two, ten,20′, 30′, 40′, and 80′ after the medication is administered. Additionally, the response to the administration of STT-I was assessed. For every time point examined, the IM group produces fewer tears on average than the IR group. The cats in the instant messaging group reacted less to the administration of STT-I. According to this study, sedatives given by the IR route may have a less common impact on tear generation than those given by the IM method. In any event, using eye lubricant is advised.

Summary:Sedatives are increasingly being used in veterinary medicine to carry out diagnostic and clinical operations. A number of anesthetic medications reduce the formation of tear flow. The therapeutic effectiveness of sedative and hypnotic drugs for novel and atraumatic delivery routes has drawn more attention in recent years. The generation of tear films in cats has never been studied.obtained sedatives using the intrarectal (IR) route. This study compares the clinical effects of an IR versus intramuscular (IM) administration of a combination of dexmedetomidine, ketamine, and midazolam on tear film flow.

Keywords : *Cats, Tear Generation, Dexmedetomidine, Ketamine, Midazolam, Sedation, Intrarectal Route, Intramuscular Route.*

INTRODUCTION

Sedative medications are frequently employed in veterinary medicine to perform minor clinical diagnostic procedures on awake animals that would be challenging to complete otherwise [1]. Despite the advice to handle cats with care, provide nursing care, and environmental guidelines [2–4], and because cats are uncooperative and extremely agitated [5], anesthesia is frequently required. The most popular methods for sedating dogs and cats are intramuscular (IM) and intravenous (IV) injection [6], notwithstanding the possibility of adverse consequences. The prevalence of malignant neoformations in cats after intramuscular injection has been documented in the literature [7, 8]. People regard intramuscular injections to be the most painful and stressful method of administration [9].Eutectic cream, a prilocaine and lidocaine combination, has been studied in veterinary medicine to lessen cats' venipuncture pain [10]. However, this isn't always feasible.because of the patient's lack of cooperation, to insert a venous catheter. Additionally, it is preferable to properly manage the venous catheter to avoid various problems such inflammation, phlebitis, and/or extravasal administration [11,12]. The effectiveness and safety of sedative and analgesic medications given to dogs and cats via different routes, including oral (OS), trans-mucosal (TM), intranasal (IN), and intrarectal (IR), have been examined

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recently [5,13–17].There aren't many published studies on the effectiveness and side effects of anesthetic and analgesic medications for the IR route. A new study demonstrates that IR treatment in cats is beneficial and has few adverse effects, such as a lowerresponse to administration in contrast to the intramuscular method [17].

The corneal and conjunctival epithelial cells' ideal extracellular environment is maintained by tear secretion [18]. In addition to their antibacterial and antinociceptive properties, tears offer a protective mechanism for the ocular surface [19,20]. The glands that produce tears withThe trigeminal nerve gives rise to the lacrimal nerve, which innervates cholinergic and adrenergic fibers [19,21]. Thus, the generation of tear films may be impacted by interactions with the autonomic nervous system. There are two ways that tears can be secreted. The avascular cornea is covered by the "basal production," a constant low-level flow that aids in preserving a suitable homeostatic equilibrium [22].The second is "reflex production," which is a noticeable, fleeting secretion brought on by mechanical stimulation of the ocular surface. This second type of tear production's function is to protect the eye, for example, by eliminating foreign objects orirritants from the surface of the eyes [22].

Kerato-conjunctivitis sicca is a pathological condition that results from a lack of tear formation and causes inflammation of the cornea and conjunctiva [23, 24]. The Schirmer Tear Test is the most popular technique for measuring tear production quantitatively.I (STT-I). The STT-I measures basal and reflex tear production in both human and veterinary medicine [18, 24]. Applying eye lubricant after sedative administration is advised to ensure corneal protection [25] since more research has been done on the relationship between sedative medications and the reduction in tear production in dogs and cats [23,25,26]. As far as the authors are aware, no research has looked into how the IR route affects cats' ability to produce tear films.The following are the study's objectives: (1) Assess tear production in cats that have been sedated with dexmedetomidine, ketamine, and midazolam following two distinct administration routes (IR vs. IM); (2) Examine how these groups respond to the STT-I implantation. The primary It is hypothesized that IR treatment, as opposed to IM administration, has a less significant effect on tear generation in cats. The other theory is that when the STT-I is administered, the IR and IM groups react in the same way.

MATERIALS AND METHODS

Animals

Twenty owned domestic shorthair cats—six females and fourteen males—participated in the study. The cats were brought to the University of Teramo's Veterinary Teaching Hospital "G. Gentile" for abdominal ultrasonography or X-ray treatments that needed chemical immobilization. After being informed, owners were requested to sign a formal consent form for Every cat signed up. The Experimental Zooprophylactic Institute of Abruzzo-Molise (CEISA) and the University of Chieti-Pescara, Teramo, L'Aquila's Committee on Animal Research and Ethics (CEISA) approved the study on March 3, 2020, under protocol n> 8. On November 10, 2021, a dedicated website (www.random.org) was used to randomly allocate cats to the groups. Two operators (ADB and MR) who were not involved in the data collection process administered the drugs.Based on clinical evaluation and the performance of standard blood test screenings (hematology and serum biochemistry), the inclusion criteria were ASA I or II. Ocular, rectal, and perineal diseases, as well as pregnant cats, were regarded as exclusion criteria. Water was kept available while the cats fasted for 12 hours before to anesthesia.till the surgery begins.

Procedure

The control group (IM group) was administered 0.003 mg kg−1 of dexmedetomidine (Dextroquillan; Fatro, Bologne, Italy) and 2 mg kg−1 of ketamine (Ketavet; MSD) intramuscularly. Dexmedetomidine 0.003 mg kg−1 (Dextroquillan; Fatro, Bologne, Italy), ketamine 4 mg kg−1 (Ketavet; MSD Animal Health, Kenilworth, NJ, USA), and midazolam 0.2 mg kg−1 (Midazolam; Pharma Hameln, Hamelin, Germany) were administered endorectally to the experimental group (IR group). The IR group received a medication mixture in the rectum using an insulin syringe without a needle (Micro-fine 1 mL; BD, New York, NY, USA), whereas the IM group received an injection on the longissimus dorsi muscle.The syringe was carefully advanced to 0.3 mL into the rectum, regardless of the quantities to be injected. All syringes were lubricated with a sterile water solution prior to IR injection. Prior to medication administration in the IR group, neither rectal emptying nor enema were performed. The day prior to the procedure, in order to rule out oculist diseases,A veterinary ophthalmologist (CP) performed an ophthalmological examination, recording the following parameters prior to the procedure: intraocular pressure, eye staining with fluorescein, dazzle test, swinging flashlight test, corneal reflex, pupillary light reflex, palpebral reflex, corneal reflex, and threat reaction.The STT-I was performed using specialized ophthalmic strips (SCH-100, Eyecare, Allahabab, India). The paper strips, which had previously been bent 90 degrees, were first positioned in the right eye and then the left.for one minute inside each cat's ventral conjunctival sac (to prevent "reflex production," the cornea was never touched). The following were the time points: 2′ (T0), 10′ (T2), 20′ (T3), 30′ (T4), 40′ (T5), and 80′ minutes after drug administration (T6), as well as 1 hour before to drug administration. At the same time points, the response to the STT-I placement was assessed. displays the

reaction score.

Statistical Analyses

An ANOVA Two-Way model for repeated test with power of 0.8, α of 0.05, and taking into account the mean and SD of the drop in tear flow in a prior study [23] was used to calculate the sample size (G*Power version 3.1.9.6; University of Düsseldorf). At least Nine cats were calculated for each group. Twenty cats in all were gathered and split up into two groups. The D'Agostino and Pearson test was used to determine whether the tear secretion data were normal, and an ANOVA Two-Way model for repeated measurements was then used to process the data. The post hoc Tukey-Kramer test was applied at several points in every group. The Chi-Square test was used to process the data pertaining to the STT-I reaction. Unless otherwise specified, the data are presented as mean ± standard error throughout the paper. When p is less than 0.05, the differences are deemed significant.

RESULTS

Twenty European shorthair cats in all were divided equally between the two groups. There are no statistically significant discrepancies between the demographic information and the ASA status classification.

For the eyes that were evaluated first, each cat's right eye, tear production was considered and examined. When repeated assessments were taken at each time point, the IR group's tear secretion did not differ significantly ($p = 0.1477$); when We used a model to analyze the data pertaining to the right eye, taking into consideration the time (T0-T6), the administration method (IM vs. IR), and the interaction between time and administration method. The results showed a significant difference, with the IM group experiencing a marked decrease in tears compared to the IR group ($p < 0.001$).

There are no appreciable variations between the right and left eyes in each group with regard to response to STT-I at T0. There were notable variations in the right eye at T2 at scores 0 and 1 ($p = 0.005$ and 0.0007, respectively) and at T3 at score 0 ($p = 0.02$).At time points T4 and T6, statistically significant variations between groups were observed in the left eyes. Specifically, T6 was significant for scores 1 and 2 ($p = 0.003$ for both scores), and T4 was significant for score 0 ($p = 0.02$). For every moment in time Bradycardia, hypotension, and/or hypoventilation were not observed in either group during the trial. Atipamezole and/or flumazenil were not administered to any cats.

DISCUSSION

The results of this study indicated that both groups of cats produced fewer tears when sedated with a combination of dexmedetomidine, ketamine, and midazolam. Only in the IM group is the drop in tear production statistically significant. Prior research on the use of sedatives in healthy cats produced findings that were comparable [23, 25]. As far as we are aware, no other research have assessed the clinical effect of intrarespiratory sedative delivery on tear formation, therefore these data cannot be compared within the literature.Cats' physiological tear production varies greatly.

Cats' physiological tear production varies greatly. Rajaei and colleagues [27] found that the average tear production in healthy cats was 14.9 ± 4.8 mm/min. Cullen and colleagues reported similar data [28], with a mean and standard deviation of 17.4 ± 4.6 mm/min.variation. Many ocular conditions, including keratoconjunctivitis sicca, can result from decreased tear production [29]. Conjunctivitis, corneal ulceration, non-ulcerative keratitis, symblepharon, and eosinophilic keratitis have all been linked to values less than 9 mm/min, according to Uhl et al. [30]. To make sure that none of these conditions affected the study's findings, a veterinary ophthalmologist evaluated the cats who were part of the study.Additionally, it has been investigated how demographic information including sex, age, weight, spaying, and neutering may impact tear production [27,31,32]. Demographic information is not regarded as an influencing factor in our study since there is no statistically significant difference between the teams. Changes in specific ocular variables during anesthesia, such as the eye's central location, the absence of the blink reflex, the decrease in corneal sensitivity, or the impairment of the tear reflex, may be linked to other causes of decreased tear production [33]. Furthermore, the central action of sedatives on the central nervous system (CNS), vasoconstriction, antinociceptive effects, changed metabolism of the gland's cells, and the modification of the cellular response to stimuli by tear cells [34,35] may be further

The Role of Anesthetic Agents on Tear Flow

Many sedative medications have been shown to decrease tear production, especially in the short term [23, 25]. As Peche and colleagues [36] also showed, this decrease in production is typically temporary. In cats, tear hypoproduction was noted between 6 and 18 hours following the conclusion of general anesthesia. How It is also unclear how anesthetics affect the formation of tears in cats and dogs. Ghaffari et al. [23] showed how acepromazine and xylazine, which are depressants, affect the production of tears in the feline species when administered intramuscularly. Di Pietro et al. [25] demonstrated in a more recent investigation that cats having castration or ovariectomy who were premedicated with medetomidine intramuscularly The medication regimen used in these investigations includes alpha-two agonists (xylazine and medetomidine, respectively). Another alpha-two analgesic, like dexmedetomidine, is suggested in our study.

The only medications given to each patient by Ghaffari et al. [23] were xylazine 2 mg kg−1 and 0.2 mg kg−1 acepromazine via the intramuscular method.collective. The xylazine-treated group's pre-administration values (T0) were different from our findings. Our findings of 9.9 ± 4.6 mm/min are lower than the 13.93 ± 1.18 mm/min values reported by Ghaffari et al. [23]. Because data collection occurs at a different time, post-administration values are more difficult to interpret.But in Ghaffari et al.'s study [23], tear production was lower in the 15th minute after delivery, at 2.18 ± 0.97 mm/min; in our study, the lowest absolute value was At minute 20, it was 4.5 ± 2.01. On the other hand, Di Pietro et al. [25] suggested an intramuscular combination of 0.08 mg kg−1 medetomidine and 5 mg kg ketamine. The dosage of dexmedetomidine employed in our study is 0.003 mg kg−1, which is substantially less than that used in the previously cited studies. In terms of tear formation and duration of effect, the distinct application of alpha-two seems to produce a more marked clinical response [37].

The clinical effects of alpha-2 agonists are dose-dependent, especially when it comes to cardiovascular, respiratory, and metabolic impacts, where the effects become more noticeable as the dosage rises.until the influence reaches a ceiling [37–39]. It is challenging to compare research from the perspective of clinical response. In any event, the studies concur on the findings (reduction in tear production), despite the noticeable differences between xylazine, medetomidine, and dexmedetomidine. Because of this, it's possible that alpha-two agonists contribute significantly to the hypoproduction of tears. Alpha-two agonists' effects on the circulatory system are thought to be the cause of the decreased tear production values. Due to the stimulation of baroreceptors and subsequent arterial hypertension brought on by peripheral vasoconstriction, alpha-2 causes dose-dependent cardiovascular effects [37, 38].Peripheral organs like the lacrimal glands receive less oxygen as a result of the centralization of blood flow, which lowers physiological activity. Alpha-adrenergic receptor postsynaptic activation at the central nervous system level may be another factor, as observed by Leonardi et al. [26] in dogs.Ketamine's effect on tear formation as a stand-alone anesthetic drug was not examined.

It is unclear if ketamine directly influences tear production, although Arnett et al. [40] assessed the reduced tear production in cats brought on by a combination of ketamine, acepromazine, and atropine (an anticholinergic drug that causes hypolacrimia). The figures given in Di Our results differ significantly from those of Pietro et al. [25], most likely as a result of the significant variation in the suggested drug dosage. Our study's suggested ketamine dosage is less than half that of the intramuscular route (2 mg kg−1 of ketamine).However, Clanachan and colleagues [41] believe that the central location of the eyeball and the elevated sympathetic nervous system may be the cause of lower tear production.tone brought on by ketamine.There are no research on how benzodiazepines affect cats' ability to produce tears.Ghaffari et al. [42] assessed the effects of a single dosage of a benzodiazepine (diazepam) and a phenothiazine (acepromazine) on tear production using the rabbit as an animal study model. Acepromazine and diazepam were given intramuscularly (IM) at the same dosage of 1 mg kg−1. According to the study, rabbits given acepromazine had noticeably lower STT-I readings at the same time points—by more than 50%.Additionally, the same study demonstrates that at T15 and T25 post-administration, the STT-I values of rabbits that were administered diazepam at T0 coincide. It is logical to conclude from this study that benzodiazepines have no discernible effect on tear production. manufacturing. It makes sense that benzodiazepines have a minor impact on the generation of tear films in both cats and rabbits, given the minor cardiovascular effects of midazolam on cats [43]. This theory is hypothetical, though. Additionally, the combination of medications that have a synergistic impact [44] may also result in less tear formation.It is still unknown what pharmacokinetic factor contributes to the IR route of administration having a less impact than the IM route. As far as the author is aware, there is just one clinical study wherein midazolam, ketamine, and an alpha-2 agonist are utilized in combination for the IR route [17]. The study shows that the IR method has clinical efficacy but a smaller cardiorespiratory impact than the IM route. Although the exact pharmacokinetic cause is unknown, the findings of this investigation also suggest that it has less of an impact on tear film production.

Tear Film Production

The creation of tear films decreased in both groups. The results for the right eye showed a statistically significant change in tear flow over time.

At the conclusion of the study, the information gathered on the left eye was not taken into account.statistical evaluation. This might have caused the left eye's "false values" to rise more than the right eye's. There could be two possible mechanisms: (1) the paper strip's placement increases reflex secretion; and (2) a moderate vagal reflex activation caused by compression on the optic nerve with parasympathetic autonomic system activation increases tear production [22,45].Compared to the IR group, the IM group has a more noticeable decrease in tear generation. With values of 3.5 ± 2.0 mm/min compared to 9.1 ± 6.9 mm/min in the IR group, the IM group shows a steep decline already at T2 and a lowest peak at T4. The Our study's IM tear values are consistent with those of Ghaffari et al. 2010 [23] and Di Pietro et al. [25]. Regarding the animals used, doses, STT-I detection period, and suggested drug combination, the study designs vary. The IR route's lower

clinical impact when compared to other routes is the reason for the discrepancy between the IM and IR group values [46]. Actually, the IR group's lowest value, 8.6 ± 4.8 mm/min, is recorded at T5, and it is still much greater than the IM group's lowest peak, which is 3.5 ± 1.6 mm/min. Additionally, Figure 1 emphasizes this observation, whereIn contrast to the IM group's "up and down" tendency, the IR ripping trend is more consistent.The differences between the two groups' T6 readings are significant even though they are not statistically significant. As a matter of fact, IM values are lower than both IR and the IM group's own baseline (T0). Thus, we can conclude that the IM's clinical impact on tear generation whereby tear readings only appear to revert to baseline levels 6–18 hours after the medication is administered. However, the IR group's T0 and T6 values overlap, indicating that the physiological tear production has recovered in The IR group is quicker.

STT-I Reaction

The data's trends deviate from the original hypothesis. At specific times, noteworthy outcomes pertaining to the STT-I reaction were discovered. In both eyes, the IM group's STT-I reaction was lower than the IR group's. The response to STT-I at T0 revealed no notable variations between the two groups. At T2 and T3, the STT-I reaction is significant in the right eye (which is the first to be evaluated in all cats for all measurements); at T4 and T6, it is significant in the left eye. Rapid onset and excellent bioavailability are characteristics of the IR route [46].Therefore, our results do not support the possibility that the IR group had a lower reaction to STT-I at earlier time points than the IM group. The data in this instance are unclear, and the theories that underlie this There may be variations in pharmacokinetic behavior. The pharmacokinetics of benzodiazepines and dissociative drugs have been studied in veterinary medicine for the IR route [47,48], but not for alpha-2 agonists. On the other hand, alpha-2 analgesics' pharmacokinetics have been thoroughly investigated for the intramuscular route [37]. One of the characteristics of alpha-2 agonists is their dose-dependent onset [37], which may also be a plausible feature for the IR route.But the literature doesn't support this. The IM group's reactivity to STT-I from the initial time points is less when the same dosage of dexmedetomidine is given. The suggested low dosage of dexmedetomidine for the IR route is taken taken into consideration in order to provide mild to moderate sedation for brief clinical and diagnostic procedures. In fact, none of the cats in the research needed additional sedation or a more complex anesthetic strategy to finish their surgeries. The onset might have been accelerated by the suggestion of a greater dosage for IR administration. It is feasible to infer a longer tail of drug action for this route because the IM group reacted less even at later time points.

There are several restrictions on this study. Selecting the ideal dosage for the study design was difficult because there was no research on IR medication administration with reference to dexmedetomidine. Cats would have experienced more noticeable clinical effects from higher dosages of the medications, but there was also a chance of unintended side effects. A It would be ideal to conduct a pharmacokinetic research on the usage of dexmedetomidine via the IR route. In any event, the suggested technique is used to guarantee brief sedation for quick procedures requiring mild to moderate analgesic coverage along with chemical immobilization. Despite this, a power estimate led to the small number of animals used in this investigation.The two groups' varying levels of sedation represent another drawback. In fact, a higher level of sedation in the IM group may be the cause of a larger tear film drop. The This cannot be ascertained because the sedation state in this trial was not evaluated. Nevertheless, the medications' sedative effects were sufficient to finish the treatments that called for chemical immobilization. Repeated measurements between the right and left eyes for each measurement could have affected the second measurement, which is another major bias of the study. In any event, the authors' focus is not on the absolute value.

CONCLUSIONS

Compared to the IM group, the use of dexmedetomidine, ketamine, and midazolam via the IR route seemed to have less of an effect on tear formation. The IR method seems to have very little effect on tear generation at the suggested dosages. The pharmacokinetic To validate these results, research on benzodiazepines, dissociative drugs, and alpha-2 agonists for the IR route is advised. The available research also suggested that cats getting anesthesia by IM or IR should utilize eye gel. Additional research is required.

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