The influence of fentanyl injection followed by infusion on the intraocular pressure, pupil size and aqueous tear production in healthy non-painful dogs

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Abstract: The goal of the presented research was to assess the influence of continuously administered fentanyl on the intraocular pressure, pupil size and aqueous tear production in dogs. A prospective, randomised, double "blind" clinical study was performed. Twenty-five non-painful dogs, 13 breeds, a body weight of 10.0 ± 5.4 kg (mean ± SD) and age of 6.5 ± 3.3 years, 12 males and 13 females with no ocular abnormalities were randomly allocated into two groups receiving an intravenous injection of saline (SAL) 0.3 ml/kg followed by an infusion 2 ml/kg/h or an intravenous injection of fentanyl (FEN) 0.005 mg/kg (diluted in 0.3 ml/kg) followed by an infusion 0.005 mg/kg/h (diluted in 2 ml/kg/h). The intraocular pressure (IOP), pupil size (PS), pulse rate (PR), respiratory frequency (f_R) and systolic and diastolic arterial pressures (SAP, DAP) were measured before (baseline) and at 2, 5, 10, 20 and 30 minutes after the premedication. The Schirmer Tear Test I (STT-I) was measured prior to and at 30 min after the premedication. The data were analysed by Bartlett's, Anderson-Darling and Dunnett's tests, the *t*-test and an analysis of variance (ANOVA) ($P < 0.05$). Relative to the baseline, in the fentanyl group, the PS was significantly decreased at all time points, the PR was significantly decreased at T_{30} and the f_R was significantly decreased at T_5, T_{10}, T_{20} and T_{30}. There were no other significant changes in the IOP, STT-I, SAP and DAP relative to the baseline. Compared to the control group, in the fentanyl group, the PS was significantly smaller at T_2, T_5, T_{10}, T_{20} and T_{30}, the PR was significantly lower at T_2, T_{20} and T_{30} and the f_R was significantly higher at T_{20}. Within thirty minutes of a constant rate infusion of fentanyl in the healthy non-painful dogs, the intraocular pressure and aqueous tear production were not affected. However, the fentanyl significantly decreased pupil size. This fact should be considered, when planning analgesia where miosis is undesirable.

Keywords: canine; analgesia; opioids; pupil diameter; CRI

Intraocular pressure (IOP) is an important parameter for the normal function of a healthy eye. The physiological value of a canine's IOP is 10–25 mmHg (Renwick 2002). In addition to many other mechanisms, IOP can also be affected by the pupil size (PS) or the drugs used (Almeida et al. 2004).

One of the undesirable reactions of the analgesics used for pain management in dogs is the elevation

of the IOP (Feldman 2015). The increase in the IOP is unacceptable in patients affected by glaucoma, a penetrating eye globe injury or undergoing intraocular surgery. Therefore, perioperative care must prevent an increase in the IOP. Especially in patients with ocular blood flow abnormalities (Jantzen 1988), it is not appropriate to use drugs (analgesics) that could increase the IOP.

A μ-opioid fentanyl is one of the most commonly used drugs of pain management in dogs (Epstein 2015). It has a fast onset and duration, as well as low incidence of cardiovascular side-effects (Grimm et al. 2005). It is administered as a single bolus or infusion. Use of fentanyl as an infusion helps maintain a stable plasma concentration with a reduction of undesirable resulting reactions caused by the readministration of boluses (Guedes 2012). Administration of fentanyl in combination with other drugs in people during the induction of anaesthesia can help prevent increases in the IOP (Fukuda 2015). Mrazova et al. (2018) described the important increases of the IOP five and ten minutes after a single bolus injection of fentanyl in dogs. However, the influence of fentanyl on the IOP after a constant rate infusion in dogs has not been described yet.

The pupil size has, among other functions, a significant effect on the IOP. In general, miosis decreases and mydriasis increases the IOP. Opioids in people and dogs tend to cause miosis (Jollife 2016).

Aqueous tear production is another important function maintaining ocular homeostasis especially in the eyelids, conjunctiva and cornea. Many opioids, including fentanyl, have been shown to reduce tear production (Biricik et al. 2004).

The goal of the presented study is to assess the influence of a fentanyl injection followed by thirty minutes of a constant rate infusion (CRI) on the IOP, PS and aqueous tear production in dogs, which has not been published yet. We hypothesised that fentanyl will increase the intraocular pressure and decrease the pupil size without affecting the aqueous tear production in dogs within thirty minutes of administration.

MATERIAL AND METHODS

The procedures described below did not exceed the commonly used clinical examinations. All the procedures were performed in accordance with the current law for animal protection and the Ethics Committee of the University. All animal owners provided consent to have their animals participate in the study. The presented study was designed as a prospective, randomised, "double-blind", placebo-controlled clinical study.

The experimental protocol was adopted and modified from a previous study (Mrazova et al. 2018) describing the influence of a single injection of medetomidine, acepromazine, fentanyl or butorphanol used for anaesthesia premedication on the IOP and pupil size in dogs.

Animals. Twenty-five client-owned healthy dogs, 13 breeds, with a body weight of 10.0 ± 5.4 kg (mean ± SD) and age of 6.5 ± 3.3 years, 12 males and 13 females were enrolled in this study. All the dogs underwent periodontal treatment under general anaesthesia. They were clinically healthy non-painful without any ocular abnormalities and designated as ASA I or II according to the American Society of Anesthesiologists (ASA). The dogs were fasted for 12 h, with free access to water prior to the anaesthesia.

A complete clinical ophthalmic examination, including slit lamp biomicroscopy, applanation tonometry, gonioscopy and a Schirmer Tear Test I (STT-I), was performed by the same experienced individual person blinded to the treatment groups. Only the dogs with an IOP measured at 15–25 mmHg prior to the sedation, with an STT-I more than 12 mm/min and without any ophthalmic abnormalities were enrolled.

To avoid the influence of breed, age or body mass on the IOP, only the dogs without any eye abnormalities weighing between 5 and 20 kg and 1 to 10 years old were enrolled. The Siberian Husky and brachycephalic breeds were also excluded, because they may have higher IOP (Taylor et al. 2007). Age is a factor that may affect the IOP (Gelatt and MacKay 1998). We also excluded too small and too large dogs to avoid a relative error in the fentanyl dosing. Likewise, dogs with an IOP outside of the ranges or any other health problems or eye pathology were excluded.

Study protocol. A randomising software (www.randomizer.org) was utilised to allocate the animals to two groups – the control (SAL, saline; *n* = 10) or the fentanyl (FEN, treatment; *n* = 15) groups. An intravenous catheter was placed into the cephalic vein in all the dogs. Subsequently, the intraocular pres-

sure (IOP), pupil size (PS), Schirmer Tear Test I, pulse rate (PR), respiratory frequency (f_R) and systolic and diastolic arterial blood pressures (SAP, DAP) were measured and recorded (baseline).

The dogs in the SAL group received a rapid injection of saline (0.9% NaCl, B. Braun) 0.3 ml/kg followed by a constant rate infusion of saline 2 ml/kg/h. The dogs in the FEN group received a rapid injection of fentanyl (Fentanyl Torrex, Torrex Chiesi) 0.005 mg/kg (diluted with saline in a total volume of 0.3 ml/kg) followed by a constant rate infusion of fentanyl 0.005 mg/kg/h (diluted with saline in a total volume of 2 ml/kg/h). The infusion was continuously administered by a syringe infusion pump (Perfusor Compact S, B. Braun) over a 30 min observation period.

Measurements. All the measurements were performed by the same person that was unaware of which drug had been administered. All the dogs were maintained in a sitting position during the measurement procedures without any manipulation, jugular vein or eye compression.

In all the dogs, the IOP, PS, PR, f_R, SAP and DAP were measured and recorded five minutes before (baseline) and two (T_2), five (T_5), ten (T_{10}), twenty (T_{20}) and thirty (T_{30}) minutes after the administration of the initial bolus followed by a constant rate infusion of fentanyl or saline. The Schirmer Tear Test I measurements were taken before the administration of the fentanyl or saline (baseline) and thirty (T_{30}) minutes thereafter.

The intraocular pressure of each dog was measured using applanation tonometry (TonoPen XL, Medtronic). Prior to each new patient measurement, a new rubber cover was placed and the tonometer was calibrated. In all the dogs, the IOP was measured on the same left eye in a sitting dog. The STT-I was performed by placing the paper strips (Schirmer Tear Test, Schering Plough Animal Health) at a distance of one-third from the lateral canthus, in the inferior conjunctival fornix for one minute in each dog. In all the patients, the STT-I was measured on the same right eye in a sitting dog. The pupil size was measured using a pupilometer (Haab´s pupilometer, Merck Sharp & Dohme). The respiratory frequency was measured by visual examination of the chest movements. The heart rate was measured by the heart sounds auscultation. The non-invasive blood pressure was measured by a cuff applied to the front limb connected to a vital function monitor (Cardel 9401, Midmark).

the cuff width was set as 40% of the circumference of the limb. The collected data included the systolic and diastolic arterial blood pressure.

All the measurements were performed in the morning after the patients' acclimatisation to the lighting conditions in a quiet room for 10 min after the intravenous catheterisation.

Statistical analysis. All the data were analysed using a GraphPad InStat 3.06 (GraphPad Software Inc.), KyPlot 2.0 beta 15 (Koichi Yoshioka) and MS Excel (Microsoft). The measured parameters – IOP, PS, STT-I, PR, f_R, SAP and DAP measured at the same time points in both groups were compared to each other. The intraocular pressure, PS, PR, f_R, SAP and DAP measured at T_2, T_5, T_{10}, T_{20} and T_{30} were compared to the baseline. The Schirmer Tear Test I measured at T_{30} was compared to the baseline as well. The Anderson-Darling and Bartlett's tests were used to confirm the normal distribution of the data and the homogeneity of variance, respectively. The parametric data are reported as the mean ± standard deviation (SD), the nonparametric data were transformed using a natural log (ln) scale and are also reported as the mean ± SD. For the multiple comparisons between the baseline and T_2, T_5, T_{10}, T_{20} and T_{30} within each group, Dunnett's test was used. For the comparisons of the STT-I between the baseline and T_{30} within each group, the dependent t-test for paired comparisons was used. All the variables between the groups were compared at each specific time point using the t-test for the unpaired comparison. The level of significance was set at $P < 0.05$.

RESULTS

We have not observed any significant differences between the SAL and FEN groups with respect to the sex, body weight, age or measured parameters at the baselines (IOP, PS, STT-I, PR, f_R, SAP or DAP).

In the fentanyl group, the IOP was maintained between 16 and 30 mmHg in all the dogs throughout the measurement time (Figure 1). Relative to the baseline, the PS decreased significantly at all the measured times (at T_2 $P = 0.0392$, at T_5 $P = 0.006$, at T_{10} $P = 0.006$, at T_{20} $P = 0.0014$, at T_{30} $P = 0.003$; Figure 2). The STT-I insignificantly decreased in the fentanyl group over 30 minutes (Figure 3). Relative to the baseline, the PR decreased at T_{30} ($P = 0.0044$; Figure 4), the f_R increased at T_5
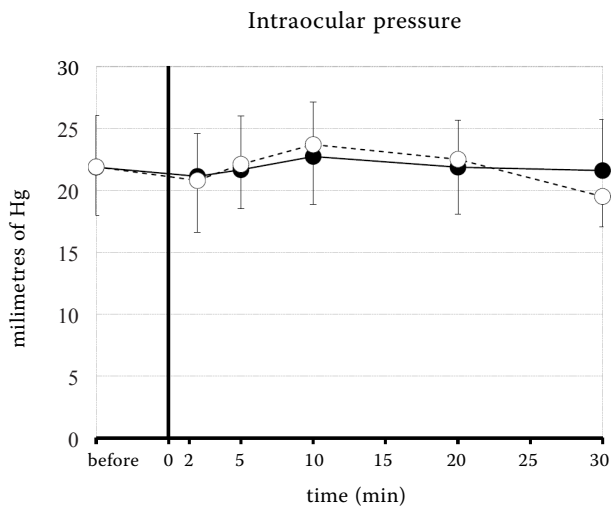
Figure 1. The intraocular pressure changes in the conscious dogs after the rapid intravenous injection followed by the continuous infusion of fentanyl (-●-) or saline (-○-) (mean ± SD)

Figure 2. The pupil size changes in the conscious dogs after the rapid intravenous injection followed by the continuous infusion of fentanyl (-●-) or saline (-○-) (* = significantly decreased compared to the baseline; ∨ = significantly decreased compared to the control group) (mean ± SD)

($P = 0.0483$), T_{10} ($P = 0.0145$), T_{20} ($P = 0.0153$) and T_{30} ($P = 0.0319$; Figure 5). There were no significant changes in the SAP and DAP relative to the baseline (Figure 6).

In the control group, no significant changes in all the measured parameters relative to the baseline were detected.

In the fentanyl group, the PS was significantly smaller compared to the control group at T_2 ($P = 0.0329$), T_5 ($P = 0.0053$), T_{10} ($P = 0.002$), T_{20} ($P = 0.0014$) and T_{30} ($P = 0.0012$; Figure 2). In the fentanyl group, the PR was lower compared to the control group at T_2 ($P = 0.0273$), T_{20} ($P = 0.0178$)

and T_{30} ($P = 0.0123$; Figure 4). In the fentanyl group, the f_R was significantly higher at T_{20} ($P = 0.0103$) compared to the control group. We have not recorded any significant differences in the other measured parameters between the groups at any other time point.

DISCUSSION

Fentanyl has a fast onset with a high analgesic potency. For a short-time analgesia, a single injection of fentanyl is used. For an extended analgesic
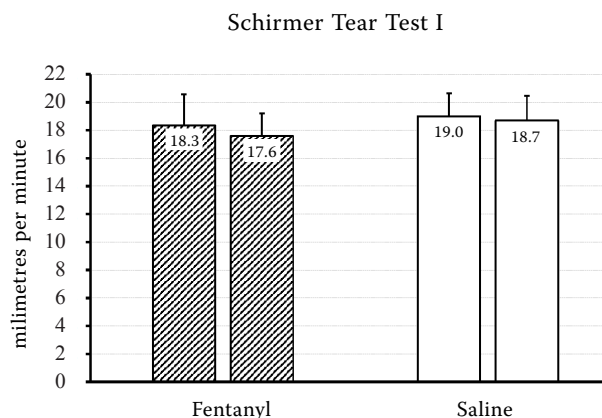

Figure 3. The Schirmer Tear Test I in the conscious dogs before (left column) and 30 minutes after the rapid intravenous injection followed by the continuous infusion (right column) of fentanyl or saline (mean ± SD)
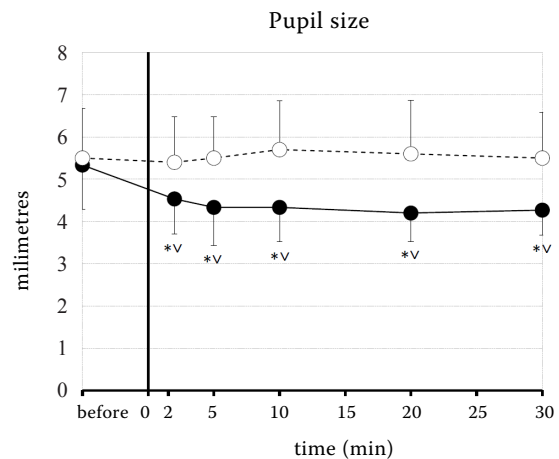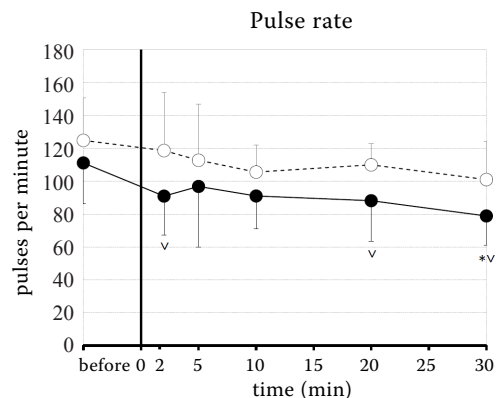

Figure 4. The pulse rate changes in the conscious dogs after the rapid intravenous injection followed by the continuous infusion of fentanyl (-●-) or saline (-○-) (* = significantly decreased compared to the baseline; ∨ = significantly decreased compared to the control group) (mean ± SD)
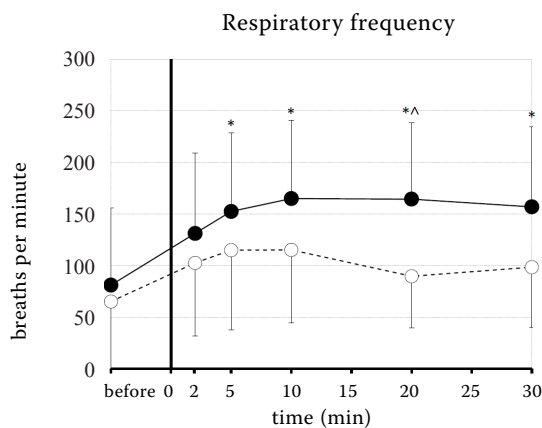
Figure 5. The respiratory frequency changes in the conscious dogs after the rapid intravenous injection followed by the continuous infusion of fentanyl (-●-) or saline (-○-) (* = significantly increased compared to the baseline, ∨ = significantly increased compared to the control group) (mean ± SD)
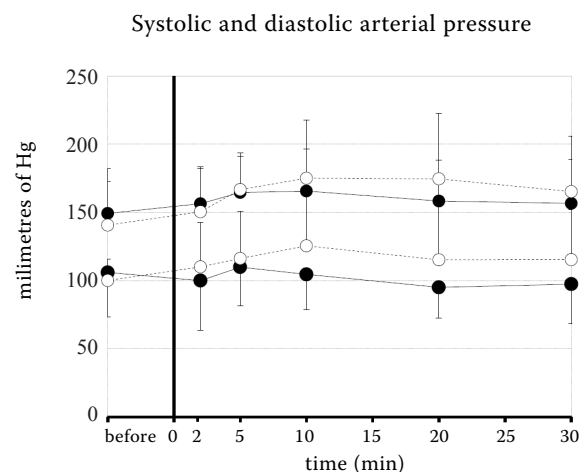

Figure 6. The systolic (upper two lines) and diastolic (lower two lines) arterial pressure changes in the conscious dogs after the rapid intravenous injection followed by the continuous infusion of fentanyl (-●-) or saline (-○-) (mean ± SD)

effect, the fentanyl must be regularly injected repeatedly. Re-administration of fentanyl may cause important respiratory depression (Yaksh et al. 1986), or be continuously infused with a reduction of the side effects. The pharmacokinetic properties of a continuously injected fentanyl dose in dogs were described by Sano et al. (2006). The continuous intravenous administration of a fentanyl dose of 0.01 mg/kg/h caused an initial increase in the plasma concentration followed up to 30 min by its decrease. Then fentanyl concentration remained fairly stable (Sano et al. 2006).

The influence of a separately injected fentanyl on the IOP in conscious dogs was described in the study (Mrazova et al. 2018). No other studies investigating the effect of fentanyl administered separately on the IOP in animals or humans have been published yet. Mrazova et al. (2018) noted a marked increase of the IOP ten minutes after a single intravenous injection of fentanyl in a dose of 0.01 mg/kg. In the current study, we used a half dose of fentanyl – 0.005 mg/kg for the induction and subsequently continued with a 0.005 mg/kg/h dose. This dose is broadly recommended and used for the continuous fentanyl administration for pain management in dogs (Sinclair 2018). The fentanyl dose administered in our study is half in comparison with the dose used in the study by Sano et al. (2006). However, the pharmacokinetics should be comparable. Although we did not measure the plasmatic concentration of fentanyl in our study, we

assume the identical situation when using a half dose of fentanyl. Important changes in the fentanyl concentration occur within 30 min after starting the continuous administration (Sano et al. 2006). After 30 min, it was supposed to be constant and its effect on the IOP, PS and cardiorespiratory variables to be without fluctuations. Therefore, we monitored the variables within 30 min of the pre-anaesthetic period only. We could no longer extend this due to the limited preoperative hospitalisation. the patients did not receive any other drugs, therefore, the IOP, PS and aqueous tear production changes caused by the fentanyl only were noted.

The IOP was maintained within 30 min of the continuous administration of the fentanyl between 16 and 30 mmHg and was without significant difference compared to the baseline or the control group. By contrast, Mrazova et al. (2018) described a significant increase in the IOP five and ten minutes after the administration of the fentanyl, when using a single injection of fentanyl in a double dose. We assume that the higher IOP may be due to the higher dose of the fentanyl used in the study by Mrazova et al. (2018). We consider a lower dose – 0.005 mg/kg/h to be safer in ophthalmic patients even with the long-term administration relative to the IOP. It can be supposed, if the IOP changes have not occurred within 30 min of the continuous intravenous administration, they will not follow later on. Other authors (Stirt and Chiu 1990; Ng et al. 2000; Sator-Katzenschlager et al. 2004; Domi 2010), who

described changes to the IOP after administration of fentanyl in people, did not use fentanyl alone. Therefore, the resulting changes in the IOP were also influenced by the concomitantly administered substances.

Fentanyl significantly decreased the PS in the dogs. Blaze et al. (2009) or Zacny et al. (1992) observed pupil constriction in dogs after the application of other μ-opioid agonist (hydromorphone, morphine) or in people after injection of fentanyl, respectively. Mrazova et al. (2018) also describes the decrease in the PS after the intravenous injection of a double dose of fentanyl. Fentanyl decreases the PS using both 0.01 mg/kg (Mrazova et al. 2018) and 0.005 mg/kg followed by 0.005 mg/kg/h within 30 min, therefore, it should be avoided when miosis is undesirable.

The influence of fentanyl on the aqueous tear production was described Biricik et al. (2004). They injected fentanyl intramuscularly in a dose of 0.01 mg/kg, after twenty minutes the STT-I decreased significantly. In our study, we used half the dose of the fentanyl intravenously followed by a continuous infusion, after thirty minutes the STT-I decreased slightly, however insignificantly. Therefore, we consider the dose 0.005 mg/kg followed by 0.005 mg/kg/h for thirty minutes safe concerning the risk of the reduction of the tear production.

Along with the eye parameters (IOP, PS and STT-I), we also monitored the vital signs (PR, f_R, SAP and DAP). We wanted to assess their dependency.

Most opioids, including fentanyl, produce, because of increased parasympathetic tone, a dose-dependent bradycardia (Laubie et al. 1974; Arndt et al. 1984; Sinclair 2018). A significant decrease in the PR was noted by Mrazova et al. (2018) ten minutes after the intravenous injection fentanyl. Also, in our study, we recorded a significant decrease in the PR after the rapid injection followed by the constant rate infusion of the half dose of fentanyl compared to Mrazova et al. (2018). However, this bradycardia does not cause a fluctuation in the IOP. The risk of bradycardia must be taken into consideration after every fentanyl administration again.

Changes in the arterial pressure have a relatively low influence on the IOP. Increased systolic arterial blood pressure induces a transient increase in the IOP due to elevating the circulating volume in the bloodstream and, thus, an increase in the blood volume in the ciliary body arteries (Macri 1961).

Although 2, 20 and 30 min after the start of the continuous fentanyl administration, we observed a significantly lower pulse rate compared to the control group, the blood pressure was not significantly different. Our results confirm Macri's (1961) theses on the minimal impact of the cardiovascular parameter changes on the IOP.

The respiratory frequency can decrease because of high or cumulative doses of fentanyl. After administration of sedative doses of fentanyl in dogs, panting is frequently observed. Hypocapnia is not necessarily present due to the dead space ventilation. Often hypercapnia is noticed (Sinclair 2018). Panting and a significant increase of the f_R was detected in the presented study and in the study of Mrazova et al. (2018) as well. Panting was also reported by Arndt et al. (1984), but with repeatedly administered fentanyl, the injected dose (0.1675 mg/kg) exceeded the dose that was used in our study or the study of Mrazova et al. (2018). Arndt et al. (1984) reported an increase in the $PaCO_2$ that may cause a rise in the IOP (Duncalf and Weitzner 1963). We did not measure the $PaCO_2$ in our study. Since we have not detected an increase in the IOP, we assume that there was no significant rise in the $PaCO_2$ caused by panting after the fentanyl administration.

Changes in blood pressure have a minimal influence on the IOP, but can induce temporary changes of the IOP (Cunningham and Barry 1986). Fentanyl can moderately increase the peripheral vascular resistance and arterial blood pressure. A decrease in the heart frequency results in the coincidental reduction of the cardiac output. These changes can lead to mild hypotension, despite cardiac contractility being preserved (Sinclair 2018). A decrease in the blood pressure was described by Grimm et al. (2005) even 60 min after a single injection of fentanyl in a dose of 0.015 mg/kg. On the contrary, Arndt et al. (1984) reported an increase in the blood pressure after the repeated administration of fentanyl (0.1675 mg/kg). We did not notice any significant changes in the systolic or diastolic blood pressure in our study. This is also one of the reasons, why the IOP values in our study have not been significantly changed throughout the observation period.

The presented study was performed on healthy non-painful dogs. The painful process induces pathophysiological changes in the patient's body, which may affect the intraocular homeostasis as well. The influence of fentanyl on the IOP in painful dogs, therefore, requires further studies.

In conclusion, within thirty minutes after a rapid injection followed by a constant rate infusion of fentanyl in healthy dogs, the intraocular pressure and aqueous tear production were not affected. However, the fentanyl significantly decreased the pupil size. This fact should be considered when planning analgesia where miosis is undesirable.

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