Article

Clinical effect of buprenorphine or butorphanol, in combination with detomidine and diazepam, on sedation and postoperative pain after cheek tooth extraction in horses

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Abstract — The objective of this study was to compare effects of butorphanol (BUT) or buprenorphine (BUP), in combination with detomidine and diazepam, on the sedation quality, surgical conditions, and postoperative pain control after cheek tooth extraction in horses, randomly allocated to 2 treatment groups (BUT: $n = 20$; BUP: $n = 20$). A bolus of detomidine (15 μg/kg, IV) was followed by either BUP (7.5 μg/kg, IV) or BUT (0.05 mg/kg, IV). After 20 min, diazepam (0.01 mg/kg, IV) was administered and sedation was maintained with a detomidine IV infusion (20 μg/kg/h), with rate adjusted based on scores to 5 variables. All horses received a nerve block (maxillary or mandibular), and gingival infiltration with mepivacaine. Sedation quality was assessed by the surgeon from 1 (excellent) to 10 (surgery not feasible). A pain scoring system (EQUUS-FAP) was used to assess postoperative pain. Serum cortisol concentrations and locomotor activity (pedometers) were measured.

Horses in BUP and BUT required a median detomidine infusion rate of 30.2 μg/kg/h (20 to 74.4 μg/kg/h) and 32.2 μg/kg/h (20 to 48.1 μg/kg/h), respectively ($P = 0.22$). Horses in the BUP group had better sedation quality ($P < 0.05$) during surgery and higher step counts ($P < 0.001$) postoperatively. Buprenorphine combined with detomidine provided a more reliable sedation than butorphanol. However, the EQUUS-FAP pain scale became unreliable because of BUP-induced excitement behavior.

Résumé — Effet clinique de la buprénorphine ou du butorphanol, en association avec la détomidine et le diazépam, sur la sédation et la douleur postopératoire après extraction de dents jugales chez le cheval. L'objectif de cette étude était de comparer les effets du butorphanol (BUT) ou de la buprénorphine (BUP), en association avec la détomidine et le diazépam, sur la qualité de la sédation, les conditions chirurgicales et la gestion de la douleur postopératoire après extraction des dents jugales chez les chevaux, répartis au hasard dans deux groupes de traitement (BUT : $n = 20$; BUP : $n = 20$). Un bolus de détomidine (15 μg/kg, IV) a été suivi soit de BUP (7,5 μg/kg, IV) soit de BUT (0,05 mg/kg, IV). Après 20 min, du diazépam (0,01 mg/kg, IV) a été administré et la sédation a été maintenue avec une perfusion IV de détomidine (20 μg/kg/h), avec un taux ajusté en fonction des scores de cinq variables. Tous les chevaux ont reçu un bloc nerveux (maxillaire ou mandibulaire) et une

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Drs. Bienert-Zeit and Kästner contributed equally to this study. FH, KH, ABZ, SK designed the study. FH carried out the clinical examinations and measurements, drafted the manuscript, created the figures, and performed the statistical analyses. MS performed the cortisol analyses. KH, ABZ, and SK critically revised the manuscript. All authors have read and approved the final version of the manuscript.

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infiltration gingivale avec de la mépivacaïne. La qualité de la sédation a été évaluée par le chirurgien de 1 (excellent) à 10 (chirurgie impossible). Un système de notation de la douleur (EQUUS-FAP) a été utilisé pour évaluer la douleur postopératoire. Les concentrations sériques de cortisol et l'activité locomotrice (podomètres) ont été mesurées.

Les chevaux en BUP et BUT ont nécessité un débit médian de perfusion de détomidine de 30,2 μg/kg/h (20 à 74,4 μg/kg/h) et 32,2 μg/kg/h (20 à 48,1 μg/kg/h), respectivement (P = 0,22). Les chevaux du groupe BUP avaient une meilleure qualité de sédation ($P < 0,05$) pendant la chirurgie et un nombre de pas plus élevé ($P < 0,001$) après l'opération. La buprénorphine associée à la détomidine a fourni une sédation plus fiable que le butorphanol. Cependant, l'échelle de douleur EQUUS-FAP est devenue peu fiable en raison du comportement d'excitation induit par le BUP.

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ARTICLE

Introduction

Cheek tooth extractions can be performed in the standing, sedated horse, thus avoiding general anesthesia and recovery (1). However, standing procedures have inherent risks of unexpected movement due to inadequate or excessive sedation. Detomidine, a potent alpha (α_2)-adrenergic agonist with dose-dependent sedation and analgesic effects, is commonly used for surgical and diagnostic procedures in the standing horse (2–4).

The combination of an α_2-agonist with an opioid is frequently used for sedation in horses. Detomidine followed by a bolus administration of either butorphanol (BUT) (5) or buprenorphine (BUP) (6) were effective for surgical procedures in the standing horse. Butorphanol is widely used in horses (7). It is a synthetic opioid receptor κ-agonist and a μ-receptor antagonist, has a dose-dependent analgesic effect lasting 15 to 90 min (8), and is used as an analgesic mainly for visceral pain (9) or in combination with α_2-agonists to enhance sedation (10). In contrast, BUP as a partial-μ-receptor agonist provides more prolonged analgesia (up to 12 h) (11) and better postoperative pain control than BUT (12). However, BUP may induce an increase in locomotor activity in the postoperative period (13).

The addition of benzodiazepines with central muscle relaxant activity for standing dental procedures can improve surgical conditions. Furthermore, for cheek tooth extractions, they can minimize chewing and tongue activity, thereby facilitating extraction (14).

Pain scoring systems to detect visceral (15), orthopedic (16), or post-castration (17) pain in horses have recently been developed. For example, the Equine Utrecht University Scale for Facial Assessment of Pain (EQUUS-FAP) focuses on facial expressions combined with pain-associated behavior (15). It has good reliability for detection and quantification of acute visceral as well as postoperative dental, ocular, or traumatic pain (15,17). In addition, blood cortisol concentrations can be used as another indicator of distress, including pain in animals (18).

The objective of this study was to compare effects of BUT or BUP in combination with detomidine and diazepam on the sedation quality, surgical conditions, and postoperative pain behavior during and after cheek tooth extraction. Based on previous studies, the authors hypothesized that BUP provides better surgical conditions and better post-operative pain control than BUT.

Materials and methods

An internal, institutional committee (University of Veterinary Medicine, Hannover) reviewed the protocol. The protocol of this study was also approved by the "Animal Welfare Committee" of the University of Veterinary Medicine, Hannover University (33.19-42502-05-16A039). All owners were informed about this study and gave their consent before sedation and the dental procedure.

Study design

Prospective, randomized, and blinded clinical investigation.

Animals

Based on previous data (14) and *a priori* power analysis (Type II error = 0.2; Type I error = 0.05), 40 separate tooth extraction events were calculated as necessary to detect a significant difference in sedation quality score, assuming a difference of 3 score points being clinically relevant.

Data were collected from 40 cheek tooth extractions of 37 horses from July 2016 to January 2017 at the Clinic for Horses, University of Veterinary Medicine Hannover, Foundation. Three horses were presented twice for cheek tooth extractions with at least 3 mo between surgeries. These 3 horses served as their own matching partners. For statistical analyses, these horses were treated as independent.

Horses received either a bolus of BUP or BUT by matched pair randomization. The main investigator (FH) was unaware of treatment and not present in the randomization phase. For randomization, breed, age, and tooth location (mandibular or maxillary) were considered. For example, a 15-year-old Icelandic horse presented for maxillary cheek tooth removal, was assigned either to treatment BUP or BUT decided by coin toss. The next Icelandic horse of similar age (± 3 y) with a diseased maxillary cheek tooth was assigned to the other treatment. Only horses with a maximum of 2 extracted teeth were included in this study. Cases with tooth removal *via* buccotomy were excluded.

Preparation and measurements

A 12-G intravenous (IV) catheter (INTRAFLON 2; VYGON GmbH & Co.KG, Aachen, Germany) was placed in the left or right jugular vein 3 h before sedation was initiated. The injection site was prepared aseptically and infiltrated with 1 mL lidocaine (Lidocainhydrochlorid 2%; bela-pharm GmbH &

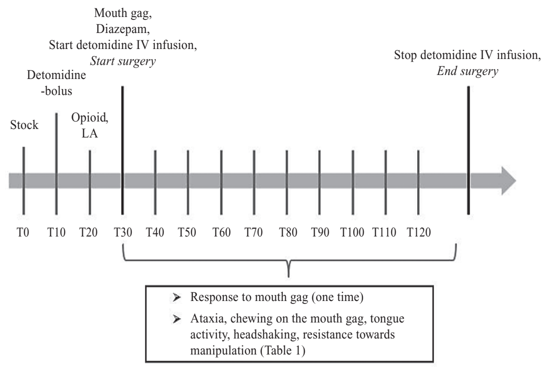

Figure 1. Pre- and intraoperative procedure. Intraoperative administrations and measurements are presented on a timeline. These measurements were used to assess the depth of sedation of 40 horses during cheek tooth extraction. Horses were sedated with a detomidine IV infusion combined with a bolus of diazepam and either butorphanol or buprenorphine.

LA — Local anesthesia.

Co.KG, Vechta, Germany) subcutaneously. One hour before sedation, all horses were treated with meloxicam (Melosolute 20 mg/mL; CP-Pharma Handelsgesellschaft mbH, Burgdorf, Germany; 0.6 mg/kg, IV). Horses were placed in stocks without sedation before the dental procedure.

Sedation protocol and surgery

After 10 min in the stocks, each horse was sedated with a bolus of detomidine (T10) (Cepesedan 10 mg/mL; CP-Pharma Handelsgesellschaft mbH, Burgdorf, Germany), 15 μg/kg, IV (Figure 1). Ten minutes later (T20), the horses received either a bolus of BUT (Butorgesic 10 mg/mL; CP-Pharma Handelsgesellschaft mbH, Burgdorf, Germany), 0.05 mg/kg, IV or BUP (Bupresol 0.3 mg/mL; CP-Pharma Handelsgesellschaft mbH, Burgdorf, Germany), 7.5 μg/kg, IV, slowly administered over 1 min. The opioids were diluted with saline to a volume of 20 mL by a person not involved in the study. At T30, all horses received a bolus of diazepam (Ziapam, 5 mg/mL; Ecuphar GmbH, Greifswald, Germany), 0.01 mg/kg, IV and a detomidine IV infusion was started (20 μg/kg/h).

A modified score for sedation depth by Müller et al (14) was used intraoperatively to adjust depth of sedation individually for each horse, depending on reaction to surgical stimulation. Five parameters (ataxia, chewing on the mouth gag, headshaking, tongue activity, and resistance towards manipulation) (Table 1) were scored from 1 (perfect tolerance) to 5 (no tolerance) by the main investigator. If a single parameter was scored ≥ 4, an additional bolus of detomidine (3 μg/kg, IV) was administered and the detomidine infusion rate was increased by 10 μg/kg/h. However, if ataxia was scored ≥ 4, the infusion rate was decreased by 10 μg/kg/h. This procedure was repeated as often as necessary (minimum 10-minute intervals) to achieve an adequate sedation level.

At T20, and immediately after the opioid bolus, the mandibular or maxillary nerve was blocked with 2 mL/100 kg mepivacaine (Scandicain 2%; AstraZeneca GmbH, Wedel, Germany), as described (19). To allow sedation and analgesia to take effect, 10 min after performing the nerve block, a mouth gag was inserted and the gingiva around the diseased tooth was infiltrated with 20 mL lidocaine (Lidocainhydrochlorid 2%; bela-pharm GmbH & Co.KG, Vechta, Germany). Oral cheek tooth extraction was done as described (20).

All extractions were performed by the same experienced surgeon (ABZ, Dipl. EVDC Equine). The surgeon was unaware of the sedation protocol and assessed the sedation quality and the surgical conditions with a Numerical Rating Scale (NRS; 1 = excellent quality to 10 = surgery not feasible/recumbency) at the end of each surgery.

Blood samples for serum cortisol concentrations

The indwelling venous catheter was used for drug administration and to withdraw all blood samples, except the sample 24 h after surgery. The first 20 mL of blood were always discarded, and then 8 mL of blood were transferred into serum tubes (VACUETTE Serum Clot Activator Tubes; Greiner Bio-One GmbH, Frickenhausen, Germany).

All horses were hospitalized the day before surgery. Surgeries were all started in the morning. Baseline blood samples were taken 3, 2, and 1 h before T0, 5 min after the start of surgery, and 3, 6, 9, 12, and 24 h after the end of surgery. The catheter was removed 12 h after surgery.

After clotting, blood samples were centrifuged at $956 \times g$ for 6 min at room temperature and serum was removed and stored at -20°C until analysis. All samples were analyzed in 1 assay. A solid-phase, competitive, chemiluminescent enzyme immunoassay (Cortisol IMMULITE; Siemens Medical Solutions, Bad Nauheim, Germany) was used to assess serum cortisol concentrations. The effective range was between 1 and 50 μg/dL with an analytic sensitivity of 0.2 μg/dL.

Postoperative behavior assessment and treatment

Pain scoring was always assessed by the main investigator, unaware of treatment, using the EQUUS-FAP (15), which involves 9 parameters, including head movement, focus on environment, muscle tone of the head, flehmen, teeth grinding, and ear position. Each parameter could be scored from 0 to 2, which results in a total score between zero (no signs of pain) and 18 points (very painful). The score was taken 24 h before surgery and 3, 6, 9, 12, and 24 h after surgery by the evaluator outside the stable, without direct interaction with the horse, and before blood sampling.

Pedometers (Pedometer by SILVA; Ex Distance, Silva Sweden AB, Bromma, Sweden) attached to a boot on 1 forelimb and 1 hind limb recorded the step counts for 12 h, 1 d before surgery and another 12 h postoperatively (21). Boots were applied when horses were back in the stall. The horses were not walked or disturbed during this time.

All horses received meloxicam (Melosus 15 mg/kg; CP-Pharma Handelsgesellschaft mbH, Burgdorf, Germany), 0.6 mg/kg, PO, q24h for 4 d following surgery. Depending on clinical signs of sinusitis or osteitis and based at clinician's discretion, horses received antibiotic or mucolytic treatment for several days.

Table 1. Modified sedation depth score (handler).

Score	Ataxia	Chewing on the mouth gag	Headshaking	Tongue activity	Defense behavior towards manipulation	
1	No ataxia	No chewing	No headshaking	No activity	No defense behavior	
2	Mild ataxia and swaying, occasionally laying against the stocks	Occasional chewing	Occasional headshaking	Occasional tongue activity	Mild defense behavior, no influence on extraction	
3	Moderate ataxia, constant leaning against the stocks, buckling of limbs	Continuously mild chewing	Continuously mild headshaking	Continuously mild tongue activity	Moderate defense behavior, mild influence on extraction	
4[a]	Severe ataxia, constant leaning against the stocks, permanent buckling of limbs[b]	Occasional severe chewing	Occasional severe headshaking	Occasional severe tongue activity	Severe defense behavior, moderate influence on extraction	
5	Recumbency	Horse does not tolerate the mouth gag	Continuously severe headshaking, no manipulation possible	Continuously severe tongue activity, no manipulation possible	Manipulation not possible, horse does not tolerate instruments for extraction	
Total score	1–5	1–5	1–5	1–5	1–5	30

[a] When one parameter was scored ≥ 4, an additional bolus of detomidine (3 μg/kg IV) was administered and the detomidine infusion rate was increased by 10 μg/kg/h.
[b] When ataxia was scored ≥ 4, the infusion rate was decreased by 10 μg/kg/h.

Data analysis

R 3.2.1 was used for all statistical analyses (RStudio, Boston, Massachusetts, USA). Normal distribution was assessed by visual assessment of qq-plots and with a Kolmogorov-Smirnov test. Data distribution allowed only nonparametric tests; therefore, results are reported as median (range).

Pain and both sedation scores and serum cortisol concentrations within treatments were analyzed by a Kruskal-Wallis test, whereas comparisons between treatments were assessed with a Mann-Whitney *U*-test, with $P < 0.05$ considered significant.

Due to the differences in duration of surgery, physiological data and subcategories of Table 1 were analyzed only until T80.

Results

Data were collected from 40 cheek tooth extractions of 37 horses, with 3 as their own matching partners. There were no significant differences between treatments regarding age, weight, gender, breed, or the extracted tooth (Table 2).

Table 2. Distribution of mean (± standard deviation) age, weight, gender and breed of horses and number of extractions of maxillary or mandibular cheek tooth.

	Buprenorphine (BUP)	Butorphanol (BUT)
Age (y)	14.1 ± 6.6	13.3 ± 5.4
Weight (kg)	477 ± 145	527 ± 102
Gender	9 mares, 11 geldings	9 mares, 11 geldings
Breed	13 Warmbloods 5 ponies 0 Thoroughbred 0 Quarter Horses 2 Icelandic Horses	11 Warmbloods 4 ponies 1 Thoroughbred 3 Quarter Horses 1 Icelandic Horses
Maxillary	15	12
Mandibular	5	8

Intraoperative data (up to T80)

All horses had a significant increase in ataxia at T10 ($P < 0.01$) compared to T0. Within horses receiving BUT, ataxia was significantly more evident at T20 compared to T10. Overall, the degree of ataxia was not different between treatments ($P = 0.055$) (Figure 2). Tongue activity ($P = 0.44$), headshaking ($P = 0.82$), chewing ($P = 0.76$), and resistance towards manipulation ($P = 0.81$) were not significantly different between treatments. Median total scores for sedation depth (handler) were not significantly different between BUP (median: 10; range: 3 to 33) and BUT (median: 11; range: 3 to 23) (Table 3).

Horses treated with BUP required a median detomidine infusion rate of 30.2 μg/kg/h (range: 20 to 74.4 μg/kg/h), whereas BUT required a median rate of 32.2 μg/kg/h (range: 20 to 48.1 μg/kg/h) ($P = 0.22$). In total, 6/40 (5/BUT and 1/BUP) horses did not tolerate surgical manipulation (continuous, severe resistance; score 4) at the beginning of surgery. However, a top-up bolus of detomidine and an increased rate of detomidine IV infusion as predefined in the protocol, resulted in scores < 3.

The surgeon's assessment of sedation quality was significantly better for BUP than BUT, but there was no significant difference in surgical conditions (Table 4).

Serum cortisol

Baseline serum cortisol concentrations were 45.5 ng/mL (range: 23.2 to 73 ng/mL) and 44.9 ng/mL (range: 18.6 to 78.8 ng/mL) in horses treated with BUT and BUP, respectively ($P = 0.34$; Figure 3).

Locomotor activity and pain scoring

Horses treated with BUP had higher step counts ($P < 0.001$) compared to horses treated with BUT at all postoperative time points (Figure 4). For EQUUS-FAP, there was a significantly

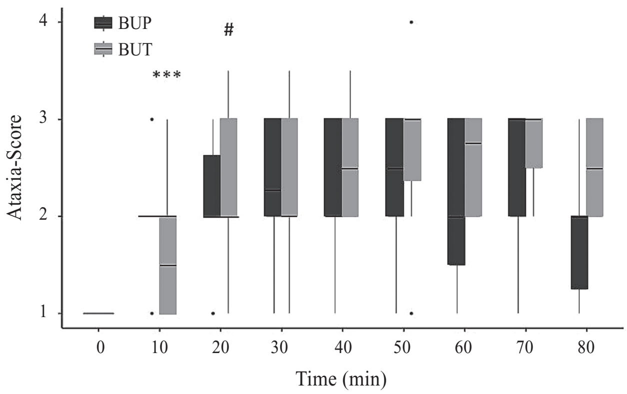

Figure 2. Ataxia. Scores for ataxia (Table 1) are presented in this figure. Before and during cheek tooth extraction in 40 horses, sedated with a detomidine IV infusion combined with a bolus of diazepam and either butorphanol or buprenorphine, ataxia was scored from 1 (no ataxia) to 5 (recumbency). Ataxia scores are presented as boxplots with median (range) BUP-buprenorphine ($n = 20$), BUT-butorphanol ($n = 20$) 0 min = baseline, 10 min = detomidine bolus, 20 min = opioid bolus (BUT or BUP), 30 min = start surgery box = interquartile range 25 to 75% • outlier *** significant difference between BUP and BUT # significant difference in group BUT from 10 to 20 min.

higher total score at 9, 12, and 24 h after surgery in horses treated with BUP (Figure 5).

Complications

All horses had mild to severe head bobbing and facial fasciculation almost immediately after administration of either opioid. Head bobbing persisted for ~15 min, but did not interfere with the surgical procedure. One horse treated with BUT sustained bilateral facial paresis during surgery. No horse had any symptoms of abdominal pain during the postoperative period.

Discussion

In the present study, detomidine and diazepam combined with either BUT or BUP provided adequate chemical restraint for cheek tooth extraction in the standing horse. Intraoperatively, sedation quality was better in horses receiving BUP. However, BUP administration resulted in postoperative increased locomotion that interfered with postoperative assessment of facial pain.

In our study, horses were given detomidine before the opioid to avoid excessive excitation; however, there were still signs of central stimulation, which did not interfere with the procedure. A consistent level of sedation was maintained during surgery with an detomidine IV infusion. Including a low dose of diazepam, for standing dental procedures reduces tongue activity and chewing, which can improve surgical conditions (14).

Sedation quality, as assessed by the surgeon, was scored significantly better in horses treated with BUP, despite no difference in the sedation depth. That both treatments had almost the same total score for sedation depth was attributed to the anesthetist intervening when sedation was not sufficient. Sedation quality (surgeon) was assessed by an NRS, which underlies a subjective bias, as the complexity and technical difficulties in extracting a tooth can indirectly influence scoring. For example, if a tooth

Table 3. Total scores as median (range) of modified sedation depth score (handler) used during surgery until T80.

	BUP[a]	BUT[b]
Ataxia	12.5 (6–23)	15 (5–23)
Chewing on the mouth gag	12 (7–21)	10 (4–22)
Headshaking	6 (3–16)	6 (3–13)
Tongue activity	11 (6–26)	11.5 (6–22)
Defense behavior towards manipulation	10.5 (3–33)	13 (4–18)
Total score	10 (3–33)	11 (3–23)

[a] Buprenorphine.
[b] Butorphanol.

Table 4. Median (range) score for sedation quality (surgeon) and surgical conditions.

	BUP[a] (n = 20)	BUT[b] (n = 20)	P-value
Quality of sedation	3 (1–7)	4 (1–7)	0.03
Surgical conditions	3 (1–5)	3 (1–7)	0.12

[a] Buprenorphine.
[b] Butorphanol.

is fragile and difficult to extract, movements by the horse subjectively deteriorate surgical conditions more than in a horse with a tooth that is easier to extract. Regardless, the surgeon was always the same and blinded to treatment, thereby minimizing bias. Individual assessment by the surgeon was not related to lower sedation depth scores or a lower detomidine infusion rate for horses treated with BUP. This observation was in accordance with another study (6), so that a subjective influence on the NRS rating is likely.

There was no significant difference between groups for assessment of surgical conditions. The regional nerve block desensitized the surgical site and if well done, may have reduced the importance of the analgesic properties of the opioid. Most horses had an acceptable level of mild aversive behavior when the surgeon started manipulation with instruments after waiting 10 min to give the anesthetic time to make an impact, with only 6/40 (5/BUT and 1/BUP) horses not tolerating surgical manipulation (continuous, severe resistance) at the beginning. For those horses, increased sedation resulted in an acceptable tolerance of manipulation.

Median detomidine infusion rate was approximately 30 μg/kg/h for both treatments to achieve adequate sedation. This seemed higher than in other studies (4,6), with a mean of 16.9 ± 4.5 μg/kg/h and a statement that a higher infusion rate was needed for dental procedures than for other types of surgeries (4). However, in that study, methadone, a synthetic opioid full μ-agonist receptor with also N-methyl-D-aspartate (NMDA) antagonist properties, was given by infusion and not as a single bolus as in our study. Furthermore, the 20-minute delay between the initial detomidine bolus and the start of the detomidine infusion in our study could also have contributed to the higher infusion rate. Behavioral and sedative effects of detomidine are greatest 15 min after treatment (22). Therefore, a delay would promote redistribution and a decrease in plasma concentrations, requiring higher infusion rates necessary to sustain adequate sedation. Furthermore, lower plasma detomidine concentrations could also be a reason for the obvious head bobbing after opioid treatment in the current study.

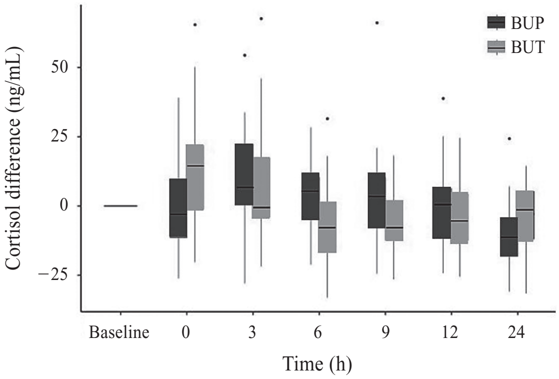

Figure 3. Serum cortisol. Serum cortisol concentration was evaluated in 40 horses presented for cheek tooth extraction. Horses were sedated with a detomidine IV infusion combined with a bolus of diazepam and either butorphanol or buprenorphine. Baseline cortisol is leveled with zero to illustrate the differences in the upcoming measurements during and post-surgery. Serum cortisol concentration is presented as boxplots with median (range) BUP-buprenorphine ($n = 20$), BUT-butorphanol ($n = 20$) 0 h = baseline, box = interquartile range 25 to 75% • outlier.

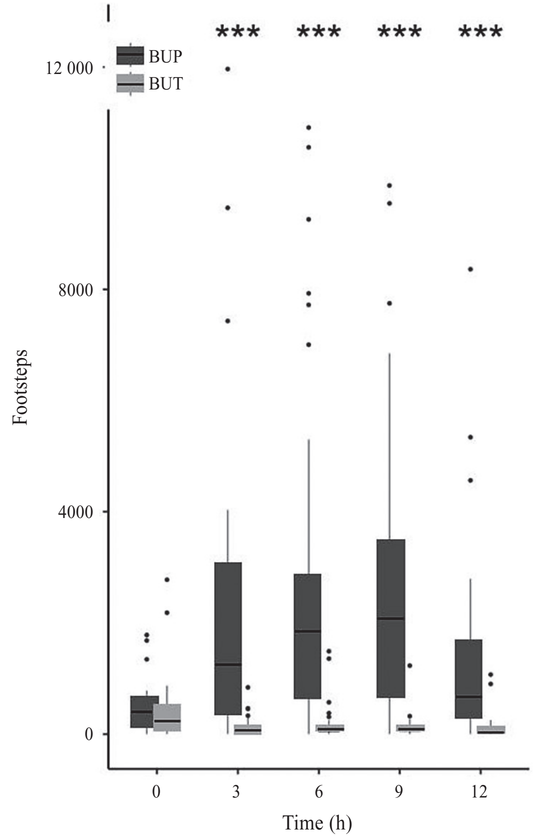

Figure 4. Footsteps. Footsteps were measured for 12 h before and after cheek tooth extraction in 40 horses to assess the locomotion dependent on the given opioid. Horses were sedated with a detomidine IV infusion combined with a bolus of diazepam and either butorphanol or buprenorphine. Results are presented as boxplots with median (range) BUP-buprenorphine ($n = 20$), BUT-butorphanol ($n = 20$) 0 h = baseline (total footsteps during 12 h pre-surgery) box = interquartile range 25 to 75% • outlier *** significant difference between BUP and BUT.

Obvious ataxia was present after detomidine administration, probably due to muscle relaxation induced by the α_2-agonist. However, this did not interfere with the surgical procedure. Although no increase of ataxia was observed immediately after BUP administration, BUT caused ataxia. Increased ataxia is described for BUT as well as for lower doses of BUP (5 μg/kg) (23). The dose of BUP used in the present study may have increased muscle tone by central stimulation, counteracting muscle relaxation induced by detomidine. Furthermore, diazepam may have influenced ataxia as well, as it acts as a central muscle relaxant (24). However, using the same dose for both treatment groups facilitated comparisons between treatments.

The main side effect in this study occurred in the postoperative period in horses receiving treatment BUP. Severe locomotor stimulation with continuous walking, up to obsessive behavior (e.g., dipping hay into water without eating it) was the most common side effect. This was evident by significantly higher step counts for the first 12 h after surgery. Although signs of locomotor stimulation have been reported in pain-free horses given buprenorphine alone or in combination with sedation and after general anesthesia up to 6 h (11,25), the intensity and duration outlasted the expectations of the authors and previous descriptions. In combination with detomidine, 5 μg/kg buprenorphine did not induce such side effects (26), but it is not clear if this low dose provided sufficient analgesia. Another approach to reduce increased locomotion in the postoperative period, is the combination of buprenorphine with acepromazine, as recommended in the package insert. The calming and neuroleptic effects of acepromazine (27) may reduce the locomotor side effects of opioids. Furthermore, acepromazine can reduce the required dose of concurrent sedatives (28). In contrast, the horses given BUT had no signs of excitation in the postoperative period. The sedative effect of the detomidine infusion probably outlasted the short duration of action of BUT (8). Regardless, due to its short half-life, we inferred that butorphanol provided limited or no analgesia in the postoperative period.

Serum cortisol concentrations were not significantly different within treatments and did not vary during the 24-hour postoperative period. However, there was a tendency for horses treated with BUT to have greater serum cortisol concentrations during surgery, implying greater stress or pain (18).

Pain scoring with the EQUUS-FAP indicated higher scores in horses treated with BUP in the later evaluation time points. EQUUS-FAP has proven good reliability for detection and quantification postoperative dental pain (17) and the combination of facial expressions with pain-associated behavior seemed to be an adequate assessment tool for the authors. However, excessive locomotor activity and central stimulation of the horses treated with BUP apparently interfered with the pain scoring based on facial signs and facial muscle tone, which could explain higher scores in this treatment group. Based on the authors' experiences and previous reported data from the group (14), this type of behavior was considered as opioid-induced and not actual pain behavior. The duration of this activity was associated with the duration of antinociceptive effects of BUP at the used dose (11). Conversely, horses treated with BUT were calm,

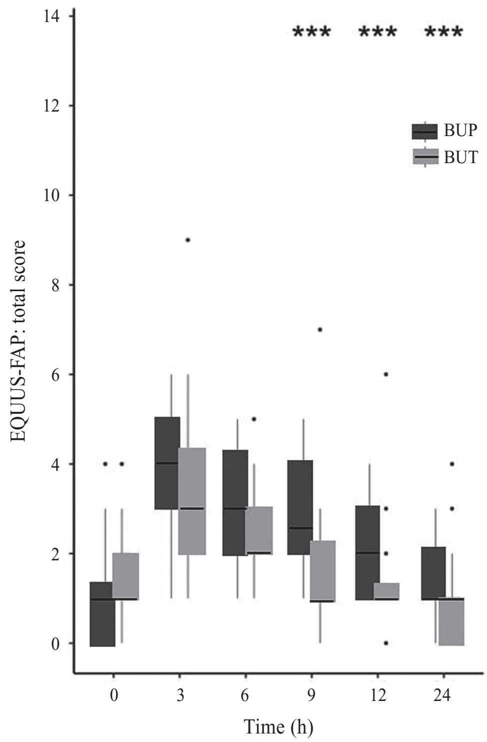

Figure 5. EQUUS-FAP. Forty horses were scored with the pain scale EQUUS-FAP (15) before and after cheek tooth extraction. Horses were sedated with a detomidine IV infusion combined with a bolus of diazepam and either butorphanol or buprenorphine. Total score of EQUUS-FAP is presented as boxplots with median (min-max) BUP-buprenorphine ($n = 20$), BUT-butorphanol ($n = 20$), 0 h = baseline, box = interquartile range 25 to 75% • outlier *** significant difference between BUP and BUT.

but seemed unresponsive to surroundings, which created the impression of painfulness. In these cases, final low scores in the EQUUS-FAP did not correlate with the subjective impression of the investigator and should not be misinterpreted as freedom from pain.

The responsiveness of the chosen pain scale EQUUS-FAP to behavioral opioid effects precluded using it for reliable post-operative pain assessment. The low pain scores before surgery were in concordance with previous observations (17). It seems that horses with longstanding dental pain do not display obvious pain behavior due to denervation (personal observation) or current pain scales may not be able to identify hidden signs of chronic pain.

Our study is not free of limitations. First, the doses of the 2 opioids were not based on equipotency. In that regard, for BUT the dose was based on current standard practice, whereas for BUP, the product label dose was chosen. Second, the effectiveness of the local block was not verified by an objective method before surgical intervention, as there is no clinically useful method that can be used reliably in sedated horses (29). That the same EVDC Diplomate performed all blocks may have minimized the risk for failure. Finally, pain assessments were performed by the evaluator standing outside the stable. Despite the absence of a direct interaction with the horse, altered horse behavior due to the presence of an observer cannot be excluded. Video analysis or retrospective photo analysis would have been a more repeatable way to observe horses (30). Regardless, the error with using a subjective scoring system was reduced by having the same observer and similar interaction with horses in both treatment groups.

In conclusion, BUP combined with detomidine provided more reliable sedation than BUT as judged by the surgeon. However, after surgery, stimulatory effects of BUP became evident and interfered with facial pain scoring. Although EQUUS-FAP has previously been used for postoperative dental pain assessment, this scoring system was not reliable in the present study, due to excessive central stimulation after administration of BUP.

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