Early analgesia after periodontal treatment in dogs: a comparison of three analgesic protocols

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ABSTRACT: The analgesic effects of carprofen, morphine and bupivacaine on early oral pain after periodontal treatment in dogs have been poorly investigated. Forty-five client-owned dogs (8.5 ± 6.4 kg and 7.8 ± 3.2 years) scheduled for periodontal treatment were allocated to carprofen, morphine and bupivacaine groups (n = 15 each). The study was designed as a prospective, randomised, double "blinded" clinical study. Carprofen (CAR, 4 mg/kg, subcutaneously) or morphine (MOR, 0.3 mg/kg, intramuscularly) was given thirty minutes before the dogs were placed under anesthesia. Bilateral maxillary and mandibular nerve blocks were performed with bupivacaine (BUP, 1 mg/kg), after the induction of anesthesia. Dogs were anaesthetised with medetomidine-propofol-isoflurane and reversal was carried out using atipamezole. Periodontal painful sub-gingival scaling was performed in all dogs. Periodontal treatment lasted for up to one hour. A modified University of Melbourne Pain Score (UMPS, 0–28 points), Visual Analog pain Scale (VAS, 0–100 mm), plasma glucose (Glu) and serum cortisol (Cor) levels were assessed before administration of analgesics (MOR-0, CAR-0, BUP-0) and two hours thereafter, that is thirty minutes after atipamezole administration (MOR-2, CAR-2, BUP-2). Analgesia rescue with tramadol (2 mg/kg intramuscularly) was provided for animals with modified UMPS over 14 or VAS over 50 points. Differences in Glu and Cor values were analysed with analysis of variance (ANOVA) for repeated measures, in UMPS and VAS over time for each group with the Friedman test and pre- and postoperatively using the Mann-Whitney U-test. Differences were considered significant at $P < 0.05$. Analgesia rescue was provided to one patient of the CAR group and one patient of the MOR group. No differences in UMPS values between groups were detected. A significant increase in VAS values after treatment was detected in all groups. Plasma glucose levels significantly increased in MOR-2 compared to MOR-0 and CAR-2. Serum cortisol levels significantly increased in MOR-2 compared to MOR-0, CAR-2 and BUP-2. The results of this study indicate that bupivacaine nerve blocks could be superior to carprofen, which in turn could be superior to morphine, for early analgesia (up to two hours) following sub-gingival scaling for periodontal treatment in dogs.

Keywords: oral pain; carprofen; morphine; bupivacaine; teeth

Oral pathology, including many painful processes, is frequent in dogs. Pain describes the physiochemical responses leading to the perception of an unpleasant sensation arising from tissue damage. Pain mechanisms, significant in oral pain, require aggressive and perhaps individual approaches to ensure maximum patient comfort. The use of pre-emptive pain management provides a consistent and predictable approach (Beckman 2006; Lavand'homme 2011). Periodontal disease or treatment causes pain and requires correct, early and intensive analgesia (Joubert and Tutt 2007).

In small animal practice the most widely used drugs for pain management are non-steroidal anti-inflammatory drugs (NSAIDs), opioids or local anaesthetics (Dzikiti et al. 2006). Non-steroidal anti-inflammatory drugs produce analgesia by inhibiting the cyclooxygenase-2 enzyme which is released at sites of tissue damage along inflammatory processes (Haas 2002). Furthermore, NSAIDs

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are involved in pain transmission both peripherally and centrally independent of the anti-inflammatory effect (Vanegas and Tortorici 2002; Kuner 2010). They block neuronal plasticity and central sensitisation. The typical NSAID commonly used in small animal practice is carprofen.

Opioids produce analgesia through their action on specific mu-, kappa- and delta-opioid receptors found in the nervous system and various tissues. Opioids, especially mu-agonists, provide the most effective pain control (Haas 2002). The most common mu-opioid used in dogs is morphine.

Local nerve block techniques provide profound and complete analgesia to the targeted tissue by blocking the generation and conduction of nerve impulses through inhibition of sodium channels. Bupivacaine is one of two local anaesthetic agents widely employed in small animal practice. It has a prolonged loading time, but also an extended duration of action (Woodward 2008).

This study was aimed at investigating the analgesic effects of carprofen, morphine and bupivacaine on early post-operative pain after periodontal treatment in dogs.

MATERIAL AND METHODS

All procedures were carried out with consent of the Animal Welfare Ethics Committee.

Animals. Forty-five adult client-owned dogs of different breeds, 25 males and 20 females, were scheduled for periodontal treatment at the Small Animal Clinic University of Veterinary and Pharmaceutical Sciences Brno. The dogs were 7.8 ± 3.2 (mean ± SD) years old and weighed 8.5 ± 6.4 kg. Apart from periodontal disease, the dogs were healthy. They were allocated randomly to one of carprofen (CAR), morphine (MOR) and bupivacaine (BUP) groups (n = 15 each). All dogs were fasted overnight prior to anaesthesia, but had free access to water.

A prospective, randomised, double blinded clinical study was performed.

Anaesthesia. Following intravenous (*i.v.*) catheterisation of the cephalic vein, the dogs were sedated with medetomidine (0.005 mg/kg *i.v.*; Domitor 1 mg/ml, Pfizer, Czech Republic). Five minutes later, anaesthesia was induced with propofol (1–3 mg/kg *i.v.*; Norofol 10 mg/ml, Norbrook, Northern Ireland) and dogs were orotracheally intubated. Anaesthesia was maintained with isoflurane (1.5–2.0 vol.%, Isofluran, Torrex Chiesi, Czech Republic) in oxygen-air (semi closed re-breathing circle system, FiO_2 = 0.6).

At the end of periodontal treatment, medetomidine was reversed by atipamezole (0.0125 mg/kg; Antisedan 5 mg/ml, Orion Pharma, Finland) administered intramuscularly (*i.m.*).

Analgesia. Thirty minutes before sedation, carprofen (4 mg/kg Rimadyl, Pfizer, Czech Republic) – CAR (n = 15) was administered subcutaneously or morphine (0.3 mg/kg, Morphin Biotika 1%, BB Pharma, Czech Republic) – MOR (n = 15) intramuscularly.

In anaesthetised dogs, intraoral bilateral maxillary and mandibular nerves blocks by intraoral injection (Beckman and Legendre 2002) were performed with bupivacaine (1 mg/kg, Marcaine 0.5%, Astra Zeneca, U.K.) in the bupivacaine group (BUP, n = 15). All nerve blocks were performed by the same person (P. Rauser).

Procedure. Periodontal disease was graded using the Periodontal Disease Index (PDI). Periodontal examination was performed in the standard way (adspection, palpation, periodontal probing, dental X-ray imaging when indicated).

Periodontal treatment started 15 min after bupivacaine was injected. It was performed using a combination of hand and power-driven instruments (Gracey curette No. 7/8, Medin, Czech Republic) was used to perform painful sub-gingival scaling) in all teeth in all of 45 dogs. Total periodontal treatment lasted up to one hour. All procedures were performed by a single dentist (P. Janalik).

Pain assessment. The Visual Analog pain Scale (VAS) represented in mm (range 0–100 mm), modified University of Melbourne Pain Scores (UMPS, range 0–28 points), plasma glucose (Glu) and serum cortisol (Cor) levels were assessed before the administration of analgesics (CAR-0, MOR-0, BUP-0), thirty minutes before induction of anaesthesia and two hours later, that is thirty minutes after atipamezole administration (CAR-2, MOR-2, BUP-2).

An analgesiometric ruler was used for VAS assessment. For modified UMPS (Hansen 2003) assessment, the following parameters were recorded: respiratory rate (0–3 points), heart rate (0–3), body temperature (0–1), pupil size (0–2), salivation (0–2), palpation response (0–2), jaws tremor (0–2), jaws self-mutilation (0–2), vocalisation (0–2), mental status (0–3), spontaneous behaviour (0–3) and manipulation response (0–3).

Blood samples for the determination of plasma glucose and serum cortisol levels were collected

from the jugular vein. Only animals with basal plasma glucose levels between 3.1–6.7 mmol/l and serum cortisol levels of between 27.61–65.5 nmol/l were included.

All modified UMPS, VAS or blood sampling was performed by a single person (M. Markova).

Rescue analgesia. Rescue analgesia with tramadol (2 mg/kg *i.m.*; Tramadol AL 100 mg, Alind Pharma, Germany) was provided for animals with a modified UMPS over 14 or VAS over 50 points. In patients in which rescue analgesia was needed, VAS or modified UMPS values were re-evaluated every hour and tramadol re-administered. Thereafter, the dogs were discharged. Tramadol (8 mg/kg orally; Tramal gtt. 100 mg/ml, Grunenthal, Germany), was prescribed and the owners used it in case of pain for rescue analgesia every four hours.

Statistical analysis. Data normality was checked using the Shapiro Wilk test and, according to these test results, differences in plasma glucose and serum cortisol levels between and within group were analysed using analysis of variance (ANOVA) for repeated measures. Modified UMPS and VAS score differences over time for each group were determined using the Friedman test, while the group comparisons pre- and postoperatively were done using the Mann-Whitney U-test. The statistical analyses were performed using commercially available software SPSS (SPSS, USA) and Microsoft Excel (Microsoft, Czech Republic). Differences were considered significant at $P < 0.05$.

RESULTS

There were no significant differences between groups with respect to gender, body mass and age or treatment time (CAR 42 ± 5 min (mean ± SD), MOR 40 ± 7 min, BUP 45 ± 5 min). No significant differences in PDI between groups was detected (in all dogs PDI grades I–IV were found).

Rescue analgesia was necessary in one patient of the CAR and in one patient of the MOR group. No follow-up rescue analgesia was needed. No significant differences were detected.

Visual Analog pain Scale values (Table 1) after treatment increased significantly in all groups compared to pre-treatment values. No other significant differences were detected.

Modified UMPS values (Table 1) after treatment increased in all groups. No significant differences were detected.

Plasma glucose levels (Table 1) significantly increased after treatment in the MOR group (MOR-2) compared to pre-treatment values (MOR-0) and in MOR-2 compared to CAR-2.

Serum cortisol levels (Table 1) significantly increased after treatment in the MOR group compared to pre-treatment values (MOR-0) and in MOR-2 compared to CAR-2 and BUP-2.

DISCUSSION

An oral pain assessment algorithm in dogs has not yet been reported. Brown et al. (2002) describe measurement of changes in the amplitude of the reflex-evoked muscle action potential elicited by non-invasive dental dolorimetry (electrical stimulation of the tooth-pulp) in anaesthetised dogs. However, the equipment necessary for these measurements is not available for common clinical practice. Therefore, we have modified the UMPS algorithm for the purposes of our study. Common oral pain symptoms – salivation, jaws tremor and jaws self-mutilation – have been added to increase the accuracy of pain assessment. Beside the subjective data mentioned above, objective values were

Table 1. Data of VAS, modified UMPS, plasma glucose and serum cortisol levels are expressed as median (range)

	VAS (mm)	UMPS (points)	Plasma glucose (mmol/l)	Serum cortisol (nmol/l)
CAR-0	4 (0–32)	1 (0–6)	6.2 (5.0–6.7)	108.0 (27.6–160.0)
CAR-2	15 (5–52)*	2 (1–7)	6.5 (5.4–8.7)	134.0 (45.1–282.0)
MOR-0	12 (0–29)	2 (0–6)	5.8 (4.8–6.7)	73.1 (31.3–157.0)
MOR-2	20 (9–55)*	3 (0–11)	6.8 (5.8–11.9)*†	236.0 (45.8–601.0)*‡
BUP-0	9 (2–26)	1 (0–5)	5.9 (5.5–6.6)	107.5 (43.5–161.0)
BUP-2	18 (2–42)*	2 (0–7)	6.6 (4.4–12.6)	84.2 (27.6–460.0)

*significant increase compared to pre-treatment values; †significant increase in MOR-2 compared to CAR-2; ‡significant increase in MOR-2 compared to CAR-2 and BUP-2

used to detect the stress response of the organism – plasma glucose and serum cortisol levels. Changes in blood glucose and plasma cortisol levels were evaluated in a study (Martins et al. 2010), that focused on pain recognition in small animals and yielded important information on pain. Catecholamine or interleukin-6 (bone inflammation) levels could also be informative regarding the quality of analgesia. Nevertheless, the required technical equipment was not available in this case.

Carprofen, morphine and bupivacaine are commonly used analgesics in dogs. The aim of this study was to investigate their efficacy when used for early analgesia after periodontal treatment. The only previous comparison of similar agents used for dental analgesia in animals (namely rats) was reported by Locher-Claus et al. (2005). They compared morphine, ibuprofen and bupivacaine before pulp exposure, which induced oral pain. Their results suggest that pre-emptive morphine or bupivacaine treatment can decrease postoperative pain significantly compared to ibuprofen administration. Such results differ with the results of our study. In dogs undergoing periodontal treatment, analgesia induced with carprofen turned out to be more effective compared to morphine. This variance could have been caused by the markedly higher dose of morphine (2.5, 5 and 10 mg/kg subcutaneously) used by Lochem-Claus et al. (2005).

Dzikiti et al. (2006) compared carprofen- and morphine-induced analgesia in dogs undergoing ovariohysterectomy. The dosage of both morphine and carprofen was similar to the one used in our study, but they did not detect any significant differences in post-operative analgesic effects between the drugs.

Subjective data values (UMPS, VAS) showed a greater range compared to the objective ones (plasma glucose, serum cortisol levels) in our study. Subjective pain assessment displays greater variability even when performed by a single person (Hardie 2000). Modified UMPS values showed no significant differences among the analgesics used. This could occur due to an inappropriate method of oral pain assessment. Moreover, the increase in UMPS values in the bupivacaine group could be false, because some animals did not show self-mutilation of the oral region due to pain, but due to the insensitivity caused by the nerve block. Another possible reason could be the short time interval between the end of the anaesthesia and second pain assessment. Therefore, in most animals the sedative effects of medetomidine could be persistent despite the antagonisation by atipamezole. Finally, we must take into consideration the possibility that minor differences in oral pain cannot be differentiated clinically.

As a stress factor, pain may be associated with increases in blood cortisol and glucose levels. Changes in these values may provide an accurate means of determining analgesic efficacy (Martins et al. 2010). In our study, blood glucose levels after periodontal treatment were significantly lower in the carprofen compared to the morphine group.

Significant lower serum cortisol levels have been reported in dogs treated with carprofen or bupivacaine compared to those treated with morphine.

Medetomidin increases glucose, but not cortisol levels. However, the doses of medetomidine used in our study should not cause a remarkable increase (Ambrisko and Hikasa 2002). Moreover, in all groups a similar dose of medetomidine was administered and the risk of error should be comparable in all groups. Morphine can increase glucose and cortisol levels (Radosevich et al. 1984), but in markedly higher doses than we used. Data concerning the effects of a medetomidine-morphine combination on glucose or cortisol levels have not yet been reported. The significant increase in glucose or cortisol values after periodontal treatment in the morphine group (Table 1, MOR-2 group), could be caused by the inferior analgesia induced by morphine or by its pharmacologic properties only.

Morphine can cause "drooling" (ptyalism) (Lang et al. 1969) and thereby an increase in the modified UMPS. We assessed salivation within our modified UMPS protocol. However, we did not detect any significant differences in the UMPS between groups, including in salivation. The hypersalivation detected in our patients appears to have been induced by periodontal treatment and pain and not as a side effect of morphine.

Rescue analgesia had to be used in two patients (one in the carprofen and one in the morphine group). These low numbers suggest that all three used analgesics induce sufficient analgesia after periodontal treatment in dogs.

Bupivacaine causes complete blockade of peripheral nociceptive input. Therefore, it should offer the best analgesia among the three agents compared in our study. The better analgesic effect of carprofen (4 mg/kg), when compared to morphine, may be due to the low dose of morphine (0.3 mg/kg). Moreover, morphine's purpose is to inhibit medium

to strong pain. Treatments performed within our study are believed to cause mild to medium pain so carprofen's analgesic effects may not be automatically superficial compared to morphine.

Carprofen's analgesic action is both peripheral and central (Yaksh and Malmberg 1993). It acts also as an antiphlogistic drug (in contrast to morphine). One of the basic components (gingivitis) or consequences (stomatitis) of periodontal disease is soft tissue inflammation, which is inhibited by carprofen (Beckham 2006). Therefore, the combined analgesic/antiphlogistic action of carprofen could have a more profound influence than the morphine analgesia.

Several studies addressing the efficacy of COX-2 inhibitors for the treatment of acute oral pain in humans have been published recently. Ibuprofen is the prototypical NSAID and represents the gold analgesic standard in humans (Huber and Terezhalmy 2006). Unless there is a specific contraindication to their use, NSAIDs are considered the drugs of choice for treating acute oral pain in human patients. Indeed, carprofen provided better analgesia than morphine in our study and can, therefore, be considered a drug of choice for analgesia in dogs. Nevertheless, with regard to multimodal analgesia in dental patients a combination of both drugs could be beneficial.

Becker (2010) reported that acute dental analgesia with NSAIDs is generally equivalent or superior to opioids. However, opioids with weaker analgesic effects (codeine, meperidine) were used in the available studies. Despite that, Becker's (2010) conclusions are in agreement with our results.

CONCLUSION

The administration of carprofen, morphine or bupivacaine for early postoperative analgesia following periodontal treatment provides sufficient analgesia in dogs. However, the results of this study indicate that bupivacaine nerve blocks could be superior to carprofen, which in turn could be superior to morphine. Nevertheless, the use of a combination of both analgesics could be more beneficial as the mutimodal approach provides considerable benefits.

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