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Effectiveness of apocynin-paeonol (APPA) for the management of osteoarthritis in dogs: comparisons with placebo and meloxicam in client-owned dogs

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Abstract

Objective: To investigate a combination of apocynin and paeonol (APPA) as an alternative to nonsteroidal anti-inflammatory drugs (NSAIDs) for the management of osteoarthritis (OA) in dogs.

Methods: Sixty client-owned dogs with OA (n=20 per group) were randomised to receive oral meloxicam (0.1 mg/kg q24h), APPA (40 mg/kg q12h), or placebo for 4 weeks. The APPA and placebo groups were double-blinded. Orthopaedic Score (OS) and Canine Brief Pain Inventory scores for Pain Severity (PS), Pain Interference (PI), and overall Quality of Life (QOL) on Days 0, 14, and 28 were examined using two-way ANOVA for repeated measures with *post hoc* Tukey's multiple comparisons test; significance was set at $p<0.05$.

Results: Fifty-five dogs completed the study. Significant improvements were seen in the meloxicam group (n=16) for OS ($p<0.01$) and QOL score ($p<0.001$). The APPA group (n=19) showed significant improvements in OS ($p<0.0001$), PS score ($p<0.01$), and PI score ($p<0.05$). On Day 28, the APPA group had significantly better OS scores for lameness at the walk and trot ($p<0.05$ each) compared with the placebo group (n=20). There were no significant differences between meloxicam and APPA groups.

Conclusion: APPA may be an effective alternative to NSAIDs in dogs with OA.

Objective

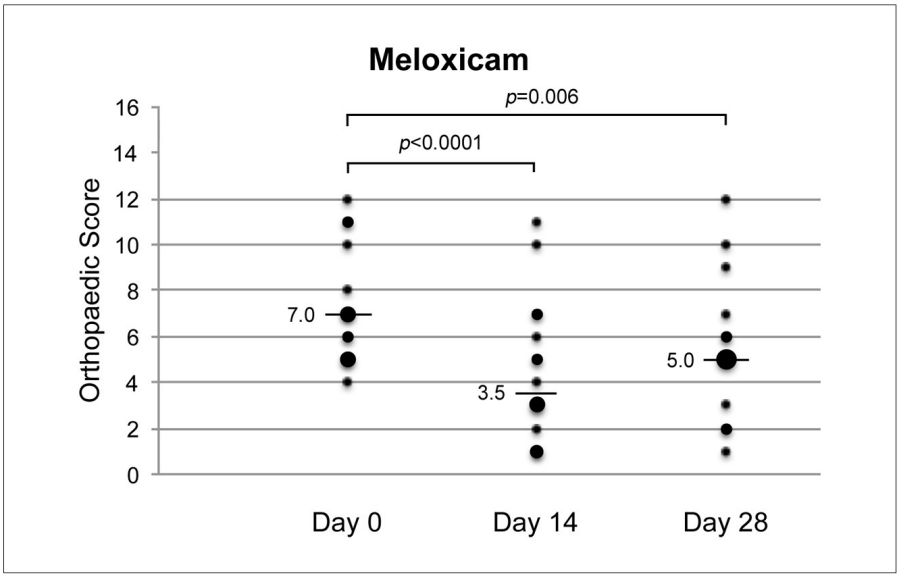
Our objective was to conduct a randomised, placebo-controlled clinical trial (RCT) to investigate APPA as a stand-alone alternative to NSAIDs, represented by meloxicam, for the management of OA in dogs. Our null hypotheses were that APPA is inferior to meloxicam and is no better than placebo for improving the signs of pain and debility in dogs with OA.

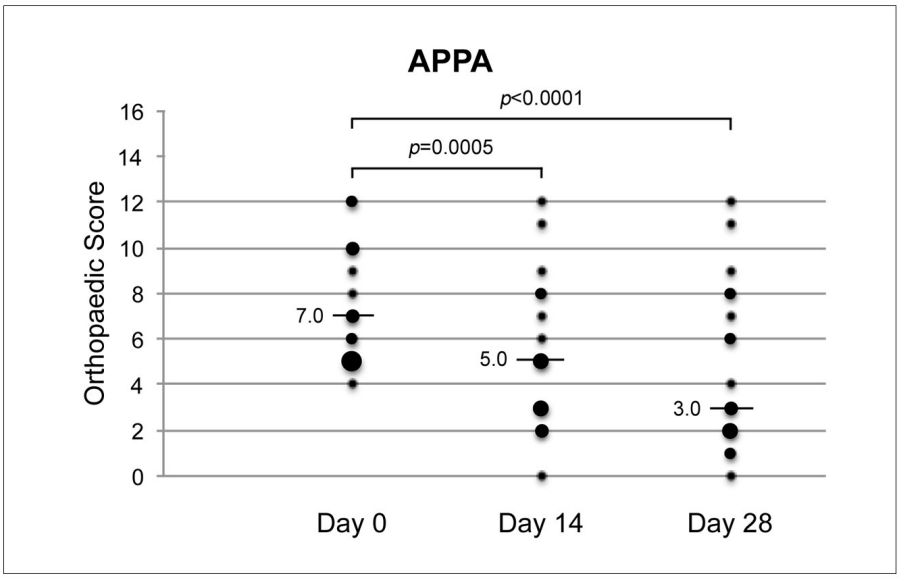
Introduction

Osteoarthritis (OA) is a common and debilitating disease in dogs. Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used to manage OA in dogs, but their efficacy is offset by concerns about safety/tolerance in some dogs [1] [2] [3]. Common adverse effects include vomiting, diarrhoea, and inappetance [3]. In addition, NSAIDs do not materially slow disease progression. Pathology-targeted treatment strategies are needed [4].

Apocynin (AP) and paeonol (PA) are plant-derived compounds with anti-inflammatory and chondroprotective effects [5] [6] [7] [8] [9] [10] [11] [12] that in combination (APPA) have potential as an alternative to NSAIDs for managing the pain and debility of OA and limiting disease progression. In a rat model of OA, APPA significantly improved weight-bearing and limited cartilage degeneration following surgically-induced meniscal injury in the knee [13].

In a clinical study of dogs with naturally-occurring OA, force-plate analysis showed that APPA significantly improved the symmetry of limb loading at the walk to values comparable with those of healthy dogs within 4 weeks [14]. However, that study did not include a placebo group and the dogs were evaluated only for gait symmetry at the walk. Hence, we conducted a placebo-controlled clinical trial of APPA in dogs with OA, evaluating various indices of comfort, function, and impact on daily life.


Meloxicam
p=0.006
p<0.0001
Orthopaedic Score
16
14
12
10
8
6
4
2
0
7.0
3.5
5.0
Day 0
Day 14
Day 28


APPA
p<0.0001
p=0.0005
Orthopaedic Score
16
14
12
10
8
6
4
2
0
7.0
5.0
3.0
Day 0
Day 14
Day 28

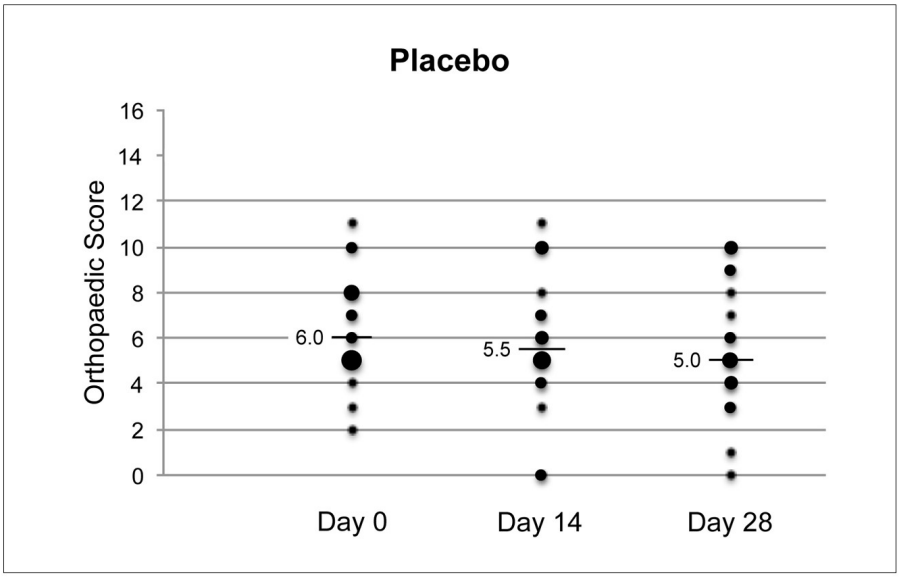

Placebo
Orthopaedic Score
16
14
12
10
8
6
4
2
0
6.0
5.5
5.0
Day 0
Day 14
Day 28

Figure Legend

Figure 1. Orthopaedic Scores during treatment for meloxicam (n=16), APPA (n=19), and placebo (n=20) groups. Median values (horizontal lines) are shown for each assessment day, and significant differences between days are shown with their *p* values (two-way ANOVA for repeated measures with *post hoc* Tukey's multiple comparisons test).
For addition information, more figures and tables are submitted as a supplementary information.

Results & Discussion

Sixty dogs were enrolled (20 dogs/group), and 55 dogs completed the study. Four dogs were withdrawn from the meloxicam group (2 for vomiting, 1 for diarrhoea, and 1 died of a cardiac tumour), and 1 dog was withdrawn from the APPA group because of vomiting. In the aforementioned clinical study, only 1/32 dogs receiving APPA was withdrawn because of vomiting [14]. In comparison, adverse effects of NSAID use reportedly occur in up to 37.5% of dogs [3].

Patient Characteristics

Baseline characteristics of all 60 dogs are summarised in Table 1, with further details in Table S2 and Table S3. Most were middle-aged or senior dogs of medium or large size. There were no significant differences in age or body weight between groups. The most commonly affected joints were the hip (38%) and the elbow (30%). Ten dogs (17%) had >1 joint clinically affected (Table S3).

Orthopaedic Score (OS)

There were no significant baseline differences in OS or its components between groups. The mean OS on Day 0 was 7.0 ± 2.4. Most dogs (72%) were mildly lame at the walk; 16 dogs (27%) were obviously lame at the walk; and 1 dog showed no apparent lameness at the walk but was mildly lame at the trot. Thus, together with age, body weight, and joint distribution, our study population is fairly representative of dogs with OA that are seen in clinical practice and are likely to be treated primarily or exclusively with an NSAID [1] [2] [3].

The OS significantly improved with treatment in the meloxicam and APPA groups but not in the placebo group (Figure 1). Significant improvements were seen in the meloxicam and APPA groups by Day 14.

When the components of the OS were examined separately, the APPA group showed significant improvements in self-directed activities (standing posture, walking, trotting) between Days 0 and 28, and had significantly better scores for lameness at the walk and trot on Day 28 compared with the placebo group (Figure 2, Table S4, Table S5). The meloxicam group showed significant improvements only in specific indices of joint pain (willingness to lift contralateral limb and pain on palpation/manipulation).

When differences in scores between Days 0 and 28 were categorised as worse, unchanged, or improved (Table 2), improvement in OS of at least 2 points occurred in 56% and 58% of dogs in the meloxicam and APPA groups, respectively, but in only 30% of dogs in the placebo group. The effect size and improvement rates in our study are similar to those reported in a larger RCT of meloxicam in dogs with OA [15].

Canine Brief Pain Inventory (CBPI)

There were no significant baseline differences in Pain Severity, Pain Interference, or overall Quality of Life scores nor their components between treatment groups.

Pain Severity (PS) score

The mean PS score on Day 0 was 4.0±1.8. The PS score significantly improved with treatment only in the APPA group (Figure 3).

When the components of the PS score were examined separately, the APPA group showed significant improvements in pain at its least and average pain between Days 0 and 28 (Figure 4, Table S6, Table S7), which may suggest a damping or moderating of the usual pain response to OA in these dogs.

The placebo group showed significant improvements in scores for current pain on Days 14 and 28 (Table S6, Table S7), illustrating the importance of including this group when using an outcome measure of this type. Not only does the placebo group account for the waxing-waning nature of OA pain, it also documents the owner's desire for improvement and, with "current pain" in particular, perhaps a desire to please the investigator by

reporting a positive outcome. Current pain may be the least useful of these PS components because this assessment was made at the veterinary clinic, where dogs are often more excited or nervous than usual, whereas the other PS indices were based on the dog's degree of pain at home and averaged over the course of a week.

Pain Interference (PI) score

Mean PI score on Day 0 was 4.3±2.0. The PI score significantly improved with treatment only in the APPA group (Figure 5). When the components of the PI score were examined separately, only the APPA group showed any significant improvement: ability to rise to standing from lying down was significantly better on Day 28 than on Day 0 (Figure 6, Table S8, Table S9).

When differences in scores between Days 0 and 28 were categorised as worse, unchanged, or improved (Table 2), improvement in PS or PI score of at least 2 points occurred in twice as many dogs in the APPA group as in the meloxicam (PS score) or placebo (PI score) group. The effect size and improvement rates for changes in PS and PI scores in the APPA group are comparable with those reported for carprofen, a widely used NSAID, in dogs with OA [16] [17].

Quality of Life (QOL) score

Mean QOL score on Day 0 was 2.9±0.8 ("good"). Only the meloxicam group showed a significant improvement in QOL score with treatment (Figure 7), although the mean score changed by <1 point (Table S10). When change in QOL score between Days 0 and 28 was categorised as worse, unchanged, or improved, 69% of dogs in the meloxicam group showed improvement of at least 1 point, whereas the rates of improvement in the APPA and placebo groups were 42% and 20%, respectively (Table 2).

Interestingly, the creator of the CBPI (DC Brown) did not use the QOL score when applying the CBPI to studies of carprofen in dogs with OA [16] [17] [18]. In fact, in a recent study, Brown concluded that the QOL domain was not sensitive to the changes associated with NSAID use in dogs with mild to moderate signs of OA [19]. While our results appear to refute that conclusion, it is worth noting that dog owners were not blinded to treatment in the meloxicam group, whereas the APPA and placebo groups were double-blinded.

Our null hypotheses, that APPA is inferior to meloxicam and is no better than placebo for managing the pain and debility of OA in dogs, are disproven. Although the findings of this study require validation in a larger group of dogs, we conclude that daily oral administration of APPA at a dosage of 40 mg/kg q12h may be effective as a stand-alone alternative to NSAIDs in dogs with OA, and we suggest that APPA is worth investigating as a pathology-targeted therapy in patients with OA.

1. The small number of dogs in each group may have prevented us from identifying some statistically significant and clinically relevant treatment differences. It was difficult to elicit the participation of even 60 owners who were willing to risk having their dogs receive placebo for 1 month. Other RCTs required the placebo group to participate without active treatment for only 7 or 14 days [15] [16] [19] [20] [21]. However, as our study showed, some of the improvement seen in the first 2 weeks of NSAID use may be lost in the following weeks, so we extended the treatment period, despite the quelling effect it had on enrolment. Our *post hoc* power calculations are summarised and discussed in the Statistical Analysis section of Methods.

2. Our outcome measures were all semiquantitative. Even so, they reflect the types of assessments made by veterinarians and dog owners in determining treatment success [15] [16] [18] [19] [20] [21] [22] [23] [24], and the CBPI has been validated in dogs with OA [16] [17].

3. The meloxicam group was not blinded. However, that may have been serendipitous: the dog owners in the meloxicam group were aware that they were administering an NSAID, so they may have had a greater expectation of efficacy, potentially making the meloxicam group an even stronger positive control.

4. We did not limit or account for different types and intensities of activity during the study period. As in people, the pain and debility of OA in dogs tends to be improved with regular, light exercise but exacerbated by unaccustomed or excessive exercise.

1. Oral APPA appears to be well tolerated at clinically effective dosages. Anecdotally and in the 52 dogs that participated in these first two clinical trials (20 dogs in the

present study and 32 dogs in the earlier study [14]), APPA has a good safety profile at oral dosages of 40-50 mg/kg q12h. Only 2/52 dogs (3.8%) were withdrawn from their respective studies, and both because of vomiting. A safety study has just been completed in rats, in which the no-adverse-effect level (NOAEL) for daily oral administration was 1,000 mg/kg. Even so, a larger clinical study of patients with OA is indicated to establish the safety and efficacy of APPA.
2. Clinical studies investigating the disease-modifying potential of APPA are indicated, based on our findings and the aforementioned experimental model of OA which showed that APPA limited cartilage degeneration following meniscal injury in rats [13].
3. Oral APPA may also improve patient well-being. Dog owners often interpret the CBPI questions about "ability to ..." as asking about the dog's *willingness* to walk, for example, and ability to *continue* walking rather than needing to stop and rest [18]. Thus, the significant improvements in PI score and ability to rise to standing from lying down, as well as the trends for improvement in ability to run and climb stairs, curbs, etc. in the APPA but not the meloxicam group suggest that APPA may be more than a mere anti-inflammatory agent, possibly having effects on mood or energy levels as well. Anecdotally, dogs often appear brighter and more engaged and energetic when treated with APPA (unpublished observations).

Additional Information

Methods and Supplementary Material

Please see https://sciencematters.io/articles/201608000001.

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CONFLICT OF INTEREST STATEMENT

Dr. Larkins is a shareholder in AKL International. Dr. King declares no conflicts of interest.

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Ethics Statement

This study was approved by the institutional ethics committee, in accordance with Good Scientific Practice guidelines and national legislation. No animals were harmed in the execution of this clinical study.

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