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Transcranial photobiomodulation therapy improves cognitive test scores in dogs with presumptive canine cognitive dysfunction: A case series of five dogs

Curtis Wells Dewey^{1,2*} , Mark Rishniw³ , Matthew Warren Brunke^{1,4} , Joyce Gerardi⁵ and Kasie Sakovitch¹

¹Elemental Pet Vets, PLLC, Freeville, New York, USA

²Department of Veterinary Clinical Sciences, Long Island University College of Veterinary Medicine, New York, USA

³Department of Clinical Sciences, College of Veterinary Medicine, Cornell University, Ithaca, New York, USA

⁴Veterinary Referral Associates, Gaithersburg, Maryland, USA

⁵Synergy Integrative Veterinary Clinic, New Bern, North Carolina, USA

Abstract

Background: Canine cognitive dysfunction (CCD) is considered the canine version of human Alzheimer's disease (AD). As with AD, CCD is a multifactorial and progressive neurodegenerative disorder for which effective treatment options are continuously being sought. Transcranial photobiomodulation (tPBMT) or transcranial laser therapy has shown promise as a treatment for cognitive impairment in rodent AD investigations and several human AD clinical trials.

Aim: The purpose of this prospective case series was to evaluate the effect of tPBMT on cognitive scores when applied to senior dogs with CCD over a 60-day period.

Methods: Five senior (>9-year-old) dogs with moderate (16–33) to severe (>33) cognitive scores were enrolled. Owners were instructed on the use of a Class IM laser device and administered a specific dose of laser energy transcranially to both sides of the patient's head, three times per week for one month and two times per week for a second month. No additional therapeutic measures aimed at enhancing cognitive ability were permitted during the 60-day evaluation time. Baseline cognitive scores were compared with scores obtained at 30- and 60-days post-treatment.

Results: Cognitive scores showed improvement in 4/5 dogs at 30 days (27.6% reduction) and all dogs at 60 days (43.4% reduction). There were no adverse effects attributable to tPBMT.

Conclusion: Results of our small case series suggest that tPBMT may improve cognitive scores in dogs with moderate to severe CCD by 30 days of application and the improvement is sustained at 60 days. Further studies are needed to ascertain optimal tPBMT protocols for CCD.

Keywords: Canine, Cognitive, Alzheimer's, Transcranial, Photobiomodulation, Laser.

Introduction

Canine cognitive dysfunction (CCD) is a progressive neurodegenerative disorder of senior dogs that is considered a naturally occurring model of human Alzheimer's disease (AD) (Landsberg *et al.*, 2012; Chapagain *et al.*, 2018; Dewey *et al.*, 2019). Numerous pathophysiologic processes have been implicated in the onset and progression of AD/CCD. These include damage to brain vasculature, neuronal mitochondrial dysfunction, toxic β -amyloid protein accumulation around neurons and blood vessels, and oxidative/inflammatory brain injury. Progressive loss of dendrites, synapses, and neurons (especially in the cerebral cortex and hippocampus) ensues over time because of these damaging events, ultimately culminating in cognitive decline (Landsberg *et al.*, 2012; Chapagain *et al.*, 2018; Dewey *et al.*, 2019; Dewey *et al.*, 2020; Ailioaie *et al.*, 2023). Photobiomodulation (PBMT) or laser therapy

entails the delivery of photons of light energy in the red to near-infrared wavelength range (approximately 600 to 1,200 nm) to tissues, to induce a positive biological response. PBMT is commonly implemented in veterinary practice, often used to decrease inflammation, accelerate healing, and attenuate pain (Anders *et al.*, 2017; Riegel and Godbold, 2017; Stephens, 2019). Transcranial PBMT (tPBMT) therapy, also known as transcranial laser therapy, involves the delivery of photons of near-infrared to infrared light from the skin surface of the scalp to the underlying brain. Several potentially beneficial molecular mechanisms of action for tPBMT have been discovered that may be beneficial for AD treatment. These mechanisms include stimulation of neuronal mitochondrial energy production (ATP synthesis), enhancement of brain blood flow, diminution of β -amyloid production and accumulation around neurons and blood vessels,

*Corresponding Author: Curtis W. Dewey, Elemental Pet Vets, PLLC, 1610 Dryden Road, Freeville, NY 13068, USA.

Email: elementalpetvets@outlook.com

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mitigation of dendrite and neuronal loss, reduced inflammatory and oxidative neuronal damage, and enhanced production of neurotrophic factors (Lapchak, 2012; Barrett and Gonzalez-Lima, 2013; Gonzalez-Lima *et al.*, 2014; Hamblin, 2016; Hennessy and Hamblin, 2017; Saltmarche *et al.*, 2017; Hamblin, 2019; Enengl *et al.*, 2020; Dewey *et al.*, 2022; Ailioaie *et al.*, 2023). There is evidence in rodent AD models and human clinical trials that tPBMT improves cognitive function (Barrett and Gonzalez-Lima, 2013; Naeser *et al.*, 2014; Saltmarche *et al.*, 2017; Salehpour *et al.*, 2017; Chan *et al.*, 2018). There is one canine study, in which single wavelength (808 nm) tPBMT was shown to improve cerebral energy production in normal laboratory beagles, as measured via magnetic resonance spectroscopy (Mintzopoulos *et al.*, 2017). To the best of the authors' knowledge, tPBMT has not been investigated as a therapeutic tool for CCD. The purpose of this open-label prospective case series was to investigate a specific tPBMT protocol for the treatment of cognitive impairment in aging dogs.

Materials and Methods

We conducted a prospective, open-label, prospective case series investigation. Senior dogs (≥ 9 years old) with a clinical diagnosis of CCD were recruited. The diagnosis of CCD was based upon signalment, history, the nature and duration of clinical signs of dysfunction, in addition to a neurologic examination. Case inclusion was limited to dogs weighing 10 kg or less, to standardize tPBMT dose administration. Other inclusion criteria included the absence of any metabolic cause for cognitive dysfunction based on recent (within 3 months) bloodwork (CBC, serum biochemistry). Clients were required to submit an informed consent form before case enrolment. Each client filled out a previously published cognitive dysfunction questionnaire (Pan, *et al.*, 2018) (Table 1) initially (baseline) and 30- and 60-days after starting tPBMT. Dog owners were instructed on the use of a Class IM laser (My Pet 2 laser, Multi Radiance Medical). Using a specific program on the laser device (Program 3), a total of 64 joules were delivered to each side of the head, as illustrated in Figure 1. This dose was approximated based on doses published for rodents and people (Gonzalez-Lima and Barrett, 2014; Salehpour *et al.*, 2017; Enengl *et al.*, 2020). The laser device (4.0 cm² aperture) was placed just rostral to the external ear (caudal aspect of the temporal fossa) and aimed toward the opposite orbit. This trajectory was chosen to target both cerebral cortical and hippocampal tissue. Wavelengths of light administered during each treatment included 660, 850, and 905 nm, at a frequency range of 1,000 to 3,000 Hz. Other tPBMT treatment parameters included the following: total power = 0.3564 W; power density = 0.0891 W/cm²; energy density = 16.04 J/cm². Each treatment was completed in 6 minutes (3 minutes per side). Owners were instructed to administer treatments 3 times per week (Monday, Wednesday and Friday) for the

Table 1. DISHAA scoring system used to assess cognitive ability in dogs. Each subcategory (bullet point) is scored as: 0 = none, 1 = mild, 2 = moderate, and 3 = severe. Total scores are assessed as: 4–15 = mild impairment, 16–33 = moderate impairment, and >33 = severe impairment.

| |
|-----------------------------------------------------------------------------------|
| DISORIENTATION |
| Gets stuck, difficulty getting around objects, goes to hinge side of door. |
| Stares blankly at walls, floor, or into space. |
| Does not recognize familiar people/familiar pets. |
| Gets lost in home or yard. |
| Less reactive to visual (sights) or auditory (sounds) stimuli. |
| INTERACTIONS (SOCIAL) |
| More irritable/fearful/aggressive with visitors, family, or other animals. |
| Decreased interest in approaching, greeting, or affection/ petting. |
| SLEEP/WAKE CYCLES |
| Pacing/restless/sleeps less/waking at night. |
| Vocalization at night. |
| HOUSE SOILING, LEARNING AND MEMORY |
| Less able to learn new tasks or respond to previously learned commands/name/work. |
| Indoor soiling of urine or stool/decreased signaling to go out. |
| Difficulty getting dog's attention/increased distraction/ decreased focus. |
| ACTIVITY |
| Decrease in exploration or play with toys, family members, other pets. |
| Increased activity including aimless pacing or wandering. |
| Repetitive behaviors, e.g., circling, chewing, licking, stargazing. |
| ANXIETY |
| Increased anxiety when separated from owners. |
| More reactive/fearful to visual (sights) or auditory (sounds) stimuli. |
| Increased fear of places/locations (e.g., new environments/going outdoors). |

first 30 days, then 2 times per week (Monday and Friday) for the following 30 days. No additional therapies aimed at improving cognitive status were permitted during the study period.

To examine the change in disorientation; interactions-social; sleep/wake cycle; house soiling, learning, and

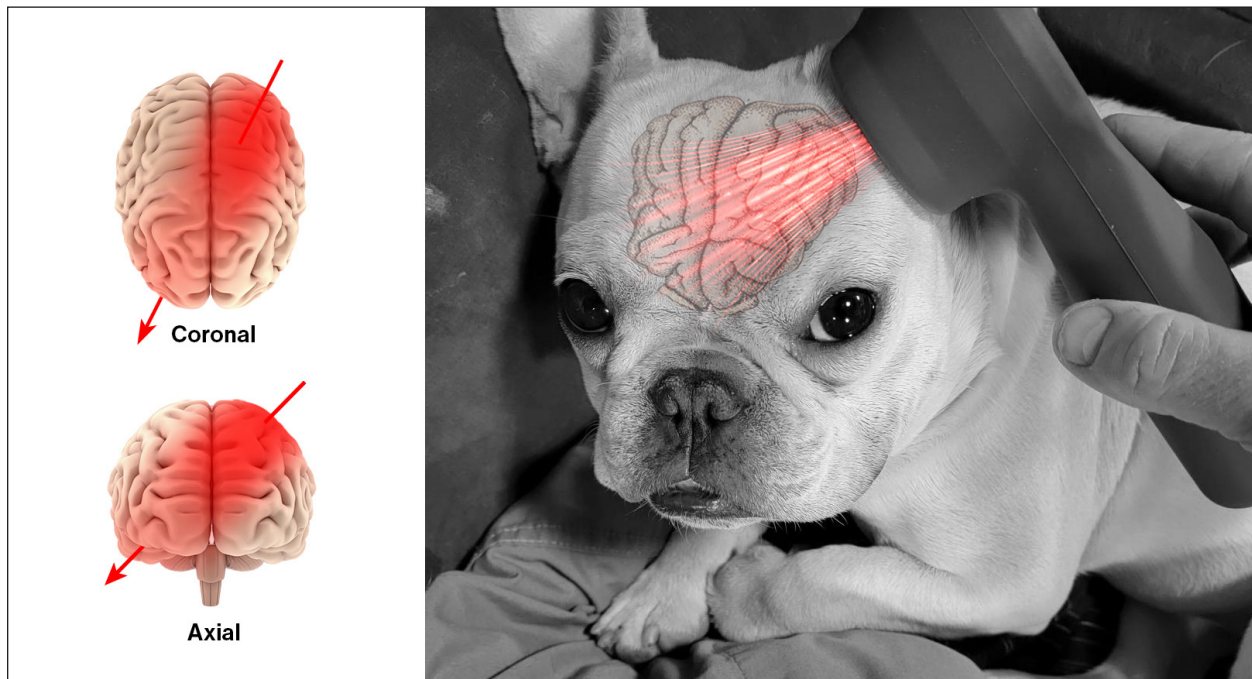


Fig. 1. Illustration depicting tPBMT delivery to a dog's brain.

memory; activity; and anxiety (DISHAA) scores, we performed a Friedman's test with post-hoc pairwise comparisons using the Dunn-Conover method.

Ethical approval

Not needed for this study.

Results

We recruited five dogs for this case series: two Chihuahuas, a Tibetan Spaniel, a Pug mix, and a Shih Tzu/Pekingese mix. Ages ranged from 11 to 15 years (median = 13 years); three were castrated males and two were spayed females. Routine hematology and biochemistry revealed no evidence of concurrent metabolic disease. DISHAA scores decreased at both 30-day and 60-day follow-up periods (Table 2, Fig. 2, $p < 0.005$). We observed no adverse effects attributed to tPBMT.

Discussion

Transcranial PBMT has the potential to improve cognition in dogs afflicted by CCD via several mechanisms, including improving neuronal mitochondrial function, reducing toxic brain amyloid load, mitigating inflammatory/oxidative brain damage, and stimulating production of neurotrophic factors (Lapchak, 2012; Barrett and Gonzalez-Lima, 2013; Gonzalez-Lima and Barrett, 2014; Hamblin, 2016; Saltmarche *et al.*, 2017; Hennessy and Hamblin, 2017; Hamblin, 2019; Enengl *et al.*, 2020; Dewey *et al.*, 2022; Ailioaie *et al.*, 2023). Our small, open-label, uncontrolled case series showed an improvement in cognitive scores for dogs with CCD treated with

tPBMT. There are several limitations to this study, including a small sample size, lack of a control (placebo) group, and lack of more rigorous methods of cognitive assessment. Because the cognitive scoring method used in our investigation engenders some level of owner subjectivity, it is possible that the perceived positive effects of tPBMT on cognition were exaggerated by owner bias. However, considering that all dogs experienced an improvement in cognitive scores, combined with the ease of home tPBMT application and lack of adverse effects, we believe our results warrant further investigation into this therapeutic modality for CCD. Anecdotally, 2 of our patients experienced documented worsening of cognitive scores within one month of discontinuing treatment; tPBMT was reinstated in one of these dogs, resulting in a return to approximately the level of cognitive improvement previously attained within one month. Further investigation into the effectiveness of tPBMT for CCD would likely benefit from the use of a control group (e.g., sham laser device) and more objective and non-biased methods of measuring cognitive function/dysfunction. Such objective methods include delayed nonmatching to positioning memory tasks, attention tasks, food-searching tasks, and problem-solving tasks (Landsberg *et al.*, 2012; Gonzalez-Martinez *et al.*, 2013; Chapagain *et al.*, 2018). Considering the progressive nature of CCD, future investigation into tPBMT for this disorder should ideally involve longer follow-up evaluation periods than presented in this study.

Table 2. Summary of pre-and post-tPBMT DISHAA scores in five dogs.

| Dog # | Signalment | Baseline DISHAA score | 30-day DISHAA score | 60-day DISHAA score | Percentage improvement (reduction) of DISHAA scores (30-/60-day) |
|-------|--------------------------------------------|-----------------------|---------------------|---------------------|------------------------------------------------------------------|
| 1 | 15 years, MC Chihuahua | 23 | 16 | 14 | 34.8% (30.4%/39.1%) |
| 2 | 11 years, 4 months, FS Shih Tzu/ Pekingese | 32 | 19 | 19 | 40.6% |
| 3 | 13 years, MC Pug | 27 | 20 | 11 | 42% (25%/59%) |
| 4 | 15 years, 1 month, MC Tibetan Spaniel | 43 | 25 | 23 | 44.5% (42%/47%) |
| 5 | 13 years, MC Chihuahua | 16 | 16 | 11 | 15.6% (0%/31.3%) |

MC: male castrated; FS: female spayed; yr: year; mo: month.

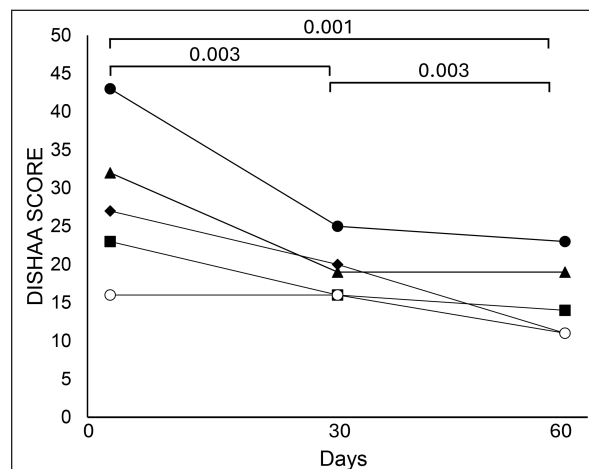


Fig. 2. DISHAA scores in five dogs treated with tPBMT. Scores at 30 and 60 days differed from day 0; scores at 60 days differed from scores at 30 days.

The ideal tPBMT treatment protocol for CCD-if one exists-remains unknown. We based our protocol on limited information from rodent AD models and human AD clinical trials (Gonzalez-Lima and Barrett, 2014; Salehpour *et al.*, 2017; Enengl *et al.*, 2020). Although we suspect that twice-a-week treatment may be sufficient, there may be more effective dosing regimens than what we used for our small clinical trial. Since PBMT is considered to have cumulative biological effects (Riegel and Godbold, 2017), it is possible that the initial month of therapy (three treatments per week) served as an induction phase, allowing for twice-a-week therapy in the second month to remain effective. Hopefully, further clinical research into various tPBMT

protocols for CCD will help to better establish the most effective protocols for dogs affected by CCD.

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Conflict of interest

There are no conflicts of interest associated with this investigation.

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Authors' contributions

Dr. Dewey was responsible for the study's inception, case recruitment, study design, and manuscript preparation. Dr. Rishniw conducted data analysis and edited the manuscript. Dr. Gerardi and Dr. Brunke were involved in case recruitment and manuscript editing. Ms. Sakovitch was responsible for client communication, data collection, and manuscript editing.

Data availability

All data from this investigation are available upon request.

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