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RESEARCH ARTICLE

Effects of Acupuncture in the Treatment of Dogs with Neurological Sequels of Distemper Virus

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Background: Acupuncture (AP) has been empirically used to relieve post-canine distemper virus (CDV) infection neurological signs in veterinary clinics.
Objectives: This clinical study aimed to investigate the effects of AP combined with electroacupuncture (EA) on neurological function in dogs infected by CDV.
Methods: Twenty-four CDV-infected dogs with neurological sequelae were recruited to receive weekly AP/EA sections for 24 weeks. Neurological improvements were assessed before each AP/EA session using a modified scoring system. Data were analyzed using the McNemar test, Friedman test, Fisher's exact test, and Kaplan-Meier curves ($p < 0.05$).
Results: Neurological scores improved from seven to 24 weeks after AP/EA treatment compared with pretreatment scores ($p < 0.001$). Significant improvements were recorded over time for functional limb recovery, cranial nerve deficits, mental status ($p = 0.025$ – 0.014), and urinary function ($p < 0.001$). Myoclonus was improved and entirely reversed in 75% and 25% of the dogs, respectively. At the end of treatment, the proportion of dogs with normal proprioception, posture, hopping ($p < 0.001$), and superficial pain sensation responses ($p = 0.004$) was greater than pretreatment values.
Conclusion: AP/EA therapy promoted significant neurological recovery in CDV-infected dogs and may be considered within the chronic phase of the disease to improve motor and sensory rehabilitation. However, these results are preliminary and must be confirmed by further investigations.

Keywords: Acupuncture, Canine distemper, Electroacupuncture, Neurological disorders, Rehabilitation

INTRODUCTION

Canine distemper virus (CDV) belongs to the family Paramyxoviridae in the genus Morbillivirus [1]. This RNA virus is associated with a severe systemic infection characterized by respiratory, gastrointestinal, and neurological signs [2,3]. Approximately 50% of CDV cases occur with systemic signs but without neurological disease [4]. However, over 30% of dogs with neurological signs have severe clinical manifestations, resulting in death or a decision for euthanasia [4,5].

During the acute phase of the disease, neurological signs result from viral replication in neurons and glial cells, leading to grey and white matter lesions with demyelination [2,3,5]. The chronic phase, also called multifocal distemper encephalomyelitis in mature dogs [3,5], may occur in dogs with a weak immune response. Viral replication overwhelms the immune system, leading to an intense and progressive inflammatory response, allowing the virus to persist outside the inflammatory lesions [3,5,6]. In these cases, astrocyte and glial cell proliferation in the white matter and production of antimyelin antibodies cause oligodendrocyte and myelin sheath destruction [5-7]. These antibodies stimulate free radical production and degrade cortical phospholipids, destroying myelin and preventing further production [8]. During this stage of disease, several neurological dysfunctions, such as cranial nerve deficits, myoclonus, tetraparesis, paraparesis, and mental abnormalities, may be

present alone or in combination [2,3,5].

Although a small percentage of dogs can spontaneously improve with time, there is currently no treatment for the neurological sequelae of CDV [4,5]. Considering that neurological disorders are closely related to poor quality of life and commonly lead to the decision to euthanize, identifying therapeutic interventions that can improve neurological rehabilitation is pivotal in CDV-infected dogs.

Acupuncture (AP), a complementary medical specialty recognized by the World Health Organization, improves motor and sensory functions and reduces neurological disorders in human and veterinary patients [9-12]. Both manual AP and electroacupuncture (EA) have been associated with functional recovery after neurological injuries [10,12]. AP can modify the sensory, motor, autonomic, visceral, hormonal, immune, and brain functions [13,14]. EA is an important AP technique used to treat neuromuscular diseases [15-18], specifically to reduce muscle atrophy and to relieve contractures, spasms, and pain [18]. According to computed tomography (CT) [19] and functional magnetic resonance imaging (fMRI) studies, EA activates brain function, maximizes neuroplasticity, and reduces inflammation [20].

Most publications regarding the neurological benefits of AP in small animals have focused on canine intervertebral disk disease (IVDD) [12,15-17]. Dogs undergoing thoracolumbar IVDD treated with EA or EA combined with prednisone demonstrated significant qualitative improvement and quicker neurological improvement than controls [16] and dogs treated with prednisone alone [17]. EA was more effective than decompression surgery for recovering motor and sensory functions in dogs with long-standing neurologic deficits caused by grade 4 or 5 thoracolumbar IVDD [12].

Although previous studies have supported AP to improve neurological rehabilitation, there is no information on the effects of this therapy in dogs with CDV sequelae. Based on the hypothesis that AP could provide temporal qualitative and quantitative improvement in chronic CDV-induced neurological deficits in dogs, this preliminary study was designed to evaluate the efficacy of AP combined with EA in this population.

MATERIALS AND METHODS

1. Study design and ethical statement

This study is a single-center, horizontal, unblended preliminary clinical trial. The study protocol was approved by the Institutional Ethical Committee for the Use of Animals in Research under protocol 1282012. All dog owners signed written informed consent forms before recruitment to participate in the study.

2. Animals

Over two years, 679 client-owned dogs with clinically suspected CDV were referred to the clinic of infectious diseases at our institution. Of these, 159 dogs were euthanized or died due to systemic complications, and the other 429 did not complete the conventional treatment (supportive care and antibiotic therapy) prior to the detection of neurological sequelae. Thus, 91 dogs were initially selected for the study, of which 23 animals died before diagnostic testing was complete. The remaining 68 dogs were screened for eligibility criteria based on physical examination, complete blood count (CBC), serum biochemical analysis, urinalysis, and neurological evaluation. After a confirmed diagnosis of CDV by reverse transcription polymerase chain reaction (RT-PCR), only 24 of the 68 dogs were enrolled in the study because 26 tested negative for CDV, and 18 that tested positive for CDV died before the beginning of AP treatment (Fig. 1). The inclusion criteria were a CDV diagnosis confirmed by RT-PCR, stable neurological clinical signs for 15 days (i.e., no change in the severity of or appearance of new neurological signs), CBC values within the reference ranges, normal appetite and defecation, and no comorbidities. The exclusion criteria included CBC abnormalities consistent with the acute phase of CDV (i.e., lymphopenia combined with leukopenia or a left-shift leukocytosis) and concomitant use of any medication.

3. AP treatment and neurological assessments

AP treatment was initiated in the chronic phase of distemper encephalomyelitis after the interruption of conventional medical treatment based on antibiotic therapy, appetite stimulants, and fluid therapy when necessary. The

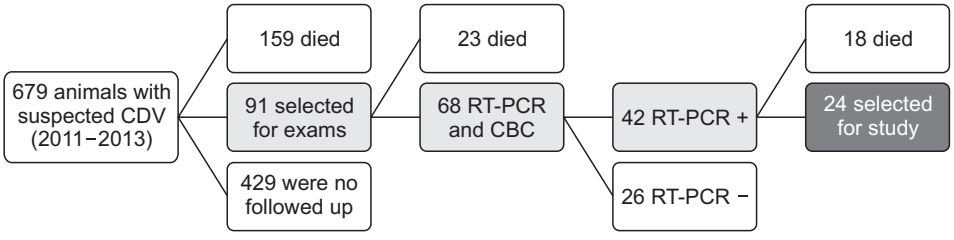

Fig. 1. Clinical trial flow diagram.

procedures were performed weekly for 24 weeks by two veterinarians with specialized training and with at least seven years of clinical AP experience. Stainless steel needles (0.25 × 30 mm or 0.15 × 30 mm; Dong Bang Acupuncture, Korea) were inserted and maintained in the bilateral Bladder (BL) 10, BL-18, BL-23, BL-40, Kidney (KI) 3, Gallbladder (GB) 20, GB-30, GB-34, GB-39, Liver (LIV) 3, Triple heater (TH) 20, Stomach (ST) 36, Large Intestine (LI) 10, Governing Vessel (GV) 14, GV-16, lumbosacral Bai-hui, and Si-shen-cong acupuncture points. At the last AP point, four needles surrounding GV-20 at 1 cm from the center were introduced [21]. EA (NKL Produtos Eletrônicos Ltda, Brusque, Brazil) was performed only at the Si-shen-cong points using a dense-disperse mixed frequency of 2 and 15 Hz for 20 minutes [12]. The intensity of the electric current was adjusted according to the individual sensitivity of the animals, gradually increasing from zero but staying below a level that caused observable muscle fasciculations.

Before the first AP treatment, a complete history was taken for each animal, along with a full physical examination and neurological evaluation to identify the affected region (brain, cerebellar, vestibular, and/or medullary regions). The exam included assessments of proprioceptive positioning, wheelbarrowing, posture, hopping, placing reaction, spinal cord reflexes (patellar, cranial tibial, and flexor reflexes of the thoracic and pelvic limbs), deep and superficial pain, muscle atrophy, cranial nerve function, and mental status. Dogs were scored based on the scoring system described in Table 1 [12].

After this initial evaluation, a weekly neurological exam was performed and scored before each AP session to assess the clinical evolution until 24 weeks of treatment or until no detection of neurological abnormalities. Treatment was considered effective when each neurological item was scored as 1, except for myoclonus, for which a score of 2 or 3 was also considered successful.

4. Statistical analysis

A sample size of 24 dogs was estimated to achieve an 80% statistical power at an alpha level of 0.05 to detect a prevalence of treatment success of 70% and treatment failure of 30%.

The Shapiro-Wilk normality test was used to evaluate the data for their distribution. McNemar's test was used to compare the proportions of neurological changes before and after treatment. A Friedman test followed by Dunn's post-test were used to compare neurological improvements over time. Fisher's exact test was applied to compare the proportions of animals showing cranial nerve changes, localization of the lesions, and presence or absence of neurologic signs before and after treatment. Kaplan-Meier curves were used to evaluate the percentage of reversal of each clinical sign during treatment. Differences were considered significant at values of $p < 0.05$.

RESULTS

Table 2 presents the baseline characteristics of the study population. The age of the animals ranged from one to 12 years (mean: 3.9 ± 2.6 years). The breeds were mixed breed (11), Poodle (5), Dachshund (2), Australian Cattle Dog (1), Toy Fox Terrier (1), Labrador Retriever (1), Rough Collie (1), Miniature Pinscher (1), and Rottweiler (1). AP treatment was initiated between one and eight months (median 2.5 ± 1.6

Table 1. Neurological scoring system used to assess CDV-infected dogs with neurological sequelae treated with acupuncture

Score	1	2	3	4	5
Paraparesis/ Paraplegia	No ataxia	Functional ambulation with ataxia	Paraparesis; standing without locomotion	Paraparesis: unable to stand	Paraplegia without deep pain
Tetraparesis/ Tetraplegia	No ataxia	Functional ambulation with ataxia	Tetraparesis: standing without locomotion	Tetraparesis: unable to stand	Tetraplegia without deep pain
Cranial nerves	No cranial nerve abnormalities	Abnormality in one cranial nerve function	Abnormalities in two or more cranial nerve function		
Behavioral changes and seizures	No behavioral changes or seizures	Behavioral changes	Seizures		
Myoclonus	Absence of myoclonus	Myoclonus only when dog is excited	Mild continuous myoclonus	Moderate continuous myoclonus	Severe continuous myoclonus
Urinary function	Normal urinary system	Urinary retention or incontinence			

Table 2. Baseline characteristics of the CDV-infected dogs with neurological sequelae treated with acupuncture

Variable	Value
Patient data	
Body weight (kg)[a]	25.1 ± 12.7
Age (years)[a]	3.9 ± 2.6
Male/Female[b]	3/5
Neurological disorders (% of dogs)	
Spinal cord signs	100.0
Paralysis	20.8
Paraparesis	20.8
Tetraparalysis	20.8
Tetraparesis	37.5
Myoclonus	50.0
Urinary retention	20.8
Brain signs (% of dogs)	
Cranial nerve deficits	75.0
Cerebrum	87.5
Cerebellum	75.0
Central Vestibular	75.0
Concomitant signs (% of dogs)	
Cerebral and cerebellar or vestibular	20.8
Cerebral and spinal	100.0
Cerebellar and vestibular	33.0
Mental status abnormalities (% of dogs)	
Vocalization or no interaction with the environment	75.0

[a]Mean ± standard deviation; [b]Number of dogs.

months) after the onset of clinical signs. The majority (79.2%; 19 of 24) of the dogs were able to start treatment two (15 of 19) or three (4 of 19) months after the onset of clinical signs; three dogs and two dogs started one month and six to eight months, respectively, after the onset of clinical signs.

The involvement of the spinal cord was detected in all dogs, with clinical signs of paralysis, paraparesis, tetraparalysis, tetraparesis, myoclonus, and urinary retention (Table 2). Locomotion was reestablished within 16 weeks of AP treatment in 75% of the dogs (Table 3). At the end of treatment, 79.2% (19 of 24) of the animals recovered functional ambulation (p = 0.025) (Fig. 2A). Myoclonus was

Table 3. Percentage (%) of treatment success over time in CDV-infected dogs with neurological sequelae treated with acupuncture

% of treatment success	25%	50%	75%	100%
	Weeks			
Locomotion	4	9	16	-
Cranial nerve deficits	3	4	5	10
Mental status	2	3	4	9
Myoclonus (return to score 1)	12	-	-	-
Myoclonus (improvement from 4 or 5 to 1, 2, or 3)	2	5	9	14
Urinary function	7	10	11	21

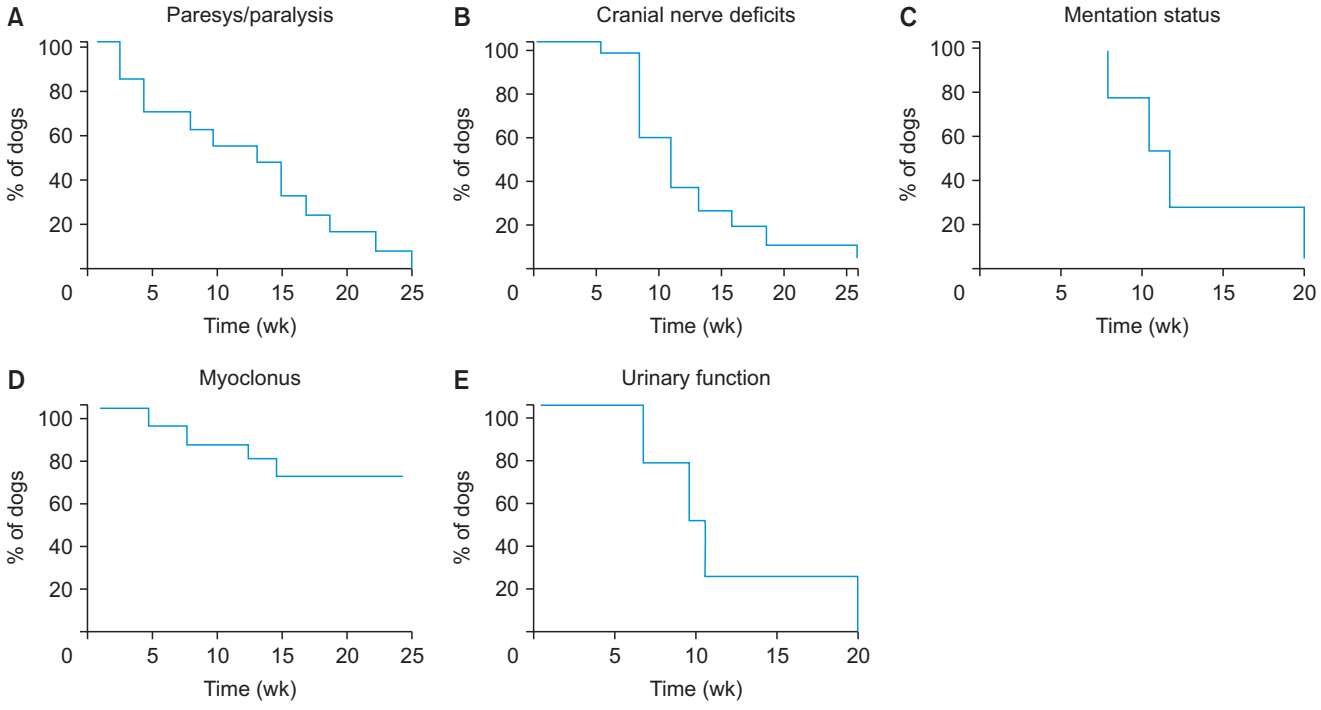

Fig. 2. Survival curve of neurological signs (A-E) in CDV-infected dogs after 24 weeks of AP treatment. Each rung represents the percentage of animals with no neurological abnormalities.

present in 50% (12 of 24) of the dogs before AP (three only in the head, two only in the pelvic limbs, two in all four limbs, one in the head and pelvic limbs, and four in the head and all four limbs). After treatment, nine of the 12 dogs (75%) still showed some degree of myoclonus (Fig. 2D), while in three of the 12 dogs (25%), myoclonus was completely reversed. Myoclonus improved from severe or moderate to mild or present only with excitement in 100% of the dogs ($p < 0.001$) (Table 3). Regarding the urinary function, 20.8% (5 of 24) of the dogs had abnormal micturition before AP (Table 2), which recovered in all animals after 21 weeks of treatment (Fig. 2E, Table 3) ($p < 0.001$).

Clinical signs consistent with the involvement of the cerebrum, cerebellum, and central vestibular system were detected in 87.5%, 75%, and 75% of the dogs, respectively (Table 2). In animals with cranial nerve deficits (18 of 24), 44.4% had concurrent deficits in cranial nerves III, IV, V, and VI, while 33.3% had deficits only in cranial nerve V. When evaluating the interaction between the affected sites, 28.6% of the dogs with cerebral involvement had concomitant cerebellar or vestibular involvement, and 100% had spinal cord involvement. Vestibular alterations were observed in 33.3% of the dogs with cerebellar lesions. No animals had seizures prior to the onset of AP therapy, but 75% (18 of 24) had altered behavior, with nocturnal vocalizations and little or no interaction with the environment or owner (Table 2). All animals recovered a normal mental status within nine weeks of treatment compared with pretreatment values ($p = 0.014$) (Table 3, Fig. 2C).

The total sum of neurological scores significantly decreased from seven to 24 weeks after AP treatment compared with pretreatment values ($p < 0.001$) (Fig. 3). By the end of treatment, the dogs showed significant increases in tactile and conscious proprioception, hopping reaction, posturing, and superficial pain sensation compared with the beginning of treatment ($p = 0.004$; $p < 0.001$) (Table 4).

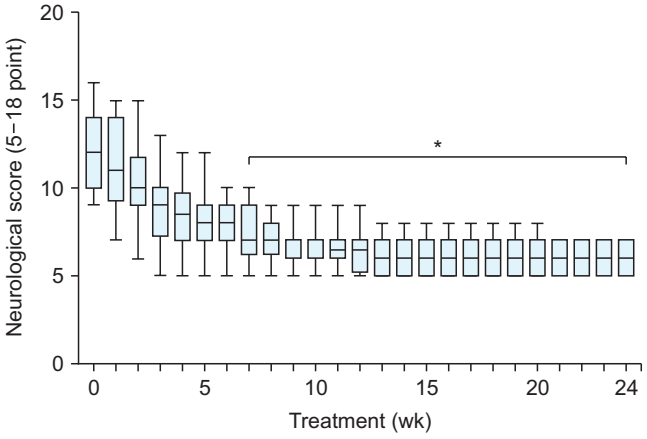

Fig. 3. Neurological scores in CDV-infected dogs after 24 weeks of AP treatment. Data are presented as medians (lines), interquartile ranges (boxes), and ranges (whiskers). *Significantly different from baseline ($p < 0.001$).

DISCUSSION

The results showing that AP/EA treatment improved neurological sequelae secondary to CDV infection in dogs confirmed the study hypothesis. These findings align with those of previous studies that reported significant motor and sensory function benefits after AP treatment as an adjunct therapy in cases of neurological disorders in humans and dogs [9-12]. AP promotes neuronal cell proliferation, regulates anti-inflammatory mediators, and inhibits microglial activation in the affected areas of the central nervous system [22,23]. These mechanisms can justify the neurological benefits found in the current study since chronic lesions caused by CDV have been associated with an intense inflammatory response with consequent severe and progressive tissue damage [3-5].

The prognosis of patients with neurological deficits caused by CDV, such as paralysis, paresis, myoclonus, and urinary retention, is often unfavorable, and conventional treatment is usually ineffective [2,3,5]. In the current study, spinal cord involvement with decreased limb motor function was observed in all patients at the beginning of treatment. Locomotion recovered progressively over time; thus, at the

Table 4. Percentage (and number) of CDV-infected dogs with neurological sequelae showing normal response of proprioception, posture reaction, hopping, flexion reflex, and pain sensation at baseline (prior to treatment) and 24 weeks after acupuncture treatment (n = 24)

	% of dogs (number)						
	Proprioception		Posture	Hopping	Flexion	Pain sensation	
	Conscious	Tactile				Superficial	Deep
Baseline	20.8 (5)	20.8 (5)	20.8 (5)	20.8 (5)	95 (23)	66.7 (16)	16.7 (4)
24 weeks	95.8 (23)	95.8 (23)	95.8 (23)	95.8 (3)	100 (24)	100 (24)	100 (24)
p-value	< 0.001		< 0.001	< 0.001	1	0.004	0.234

end of treatment, 79.2% of the dogs showed recovery of ambulation, indicating that AP was an effective therapy to promote functional rehabilitation. These findings may be attributed to the inclusion of EA in our treatment protocol because this technique may improve neuroplasticity, as demonstrated in dogs suffering from IVDD [12]. Furthermore, a study involving a murine model of spinal cord injury demonstrated neuroprotective effects following EA application, with a reduction in apoptotic cell death of neurons and oligodendrocytes and decreased expression of proinflammatory cytokines, which was associated with improved functional recovery [23]. The stimulation of specific acupoints in the present study, such as GB-30, GB-34, GB-39, ST-36, BL-18, BL23, and BL-40, may also have contributed to the functional rehabilitation because these points have been associated with motor and sensory recovery in dogs suffering from spinal cord injury [12,15-17].

The incidence of myoclonus associated with spinal cord lesions ranges between 33% and 75% [2,5]. Pharmacologic treatment of myoclonus, such as the use of clonazepam, is often unsuccessful [5]. This is likely because the myoclonus produced by CDV is not cortical, as in humans, where GABA is the most important inhibitor neurotransmitter, but spinal, where glycine is more important [4]. Intravenous boluses of lidocaine may temporarily reduce or inhibit myoclonus. This is likely the result of an interaction between central and peripheral voltage-gated Na^+ channels, affecting peripheral and central nerve endings to reduce postsynaptic depolarization in the spinal cord and central hyperexcitability [24]. However, long-term administration of intravenous lidocaine is unfeasible. Schubert et al. [25] reported successful treatment of a 13-year-old dog that was non-ambulatory due to myoclonus secondary to CDV; functional ambulation was regained after two applications of botulinum toxin in the affected muscles. In our study, myoclonus improved in 100% of the dogs, of which 25% were completely cured. These findings are promising since myoclonus is one of the most debilitating clinical signs of CDV and is often considered irreversible [2]. Our results may change the paradigm that a cure for myoclonus is impossible, showing that AP is an important therapeutic tool.

Bladder function was also reestablished in 100% of the dogs within 21 weeks of treatment. This response may be related to the modulating effect triggered by the BL-23 acupoint, located between the L2 and L3 vertebrae, which can influence the sympathetic innervation of the bladder through the hypogastric nerve, which originates between L1-L3 in dogs [25]. As bladder sphincter relaxation is controlled by sympathetic fibers [25,26], stimulation of BL-23 may abate urinary retention. In Eastern medicine, BL-23 is the association point of the Kidney, the organ responsible for maintaining the caudal sphincter tone, and seems to be important in treating urinary retention in CDV [21]. Humans with multiple sclerosis with demyelination similar to that caused by CDV also experience bladder function impairment that can be reversed by AP/EA, similar to the findings in this study. No recurrence or cystitis was noted during a 6-month follow-up [27].

When considering brain signs, 75% of the dogs in this study exhibited an abnormal mental status with nocturnal vocalizations, little interaction with the environment, and disorientation. In 100% of the dogs, the recovery of mental status may be partially attributed to the stimulation of specific acupoints such as KI-3 and ST-36, which are apparently involved with cognitive functions [28-30]. Our results are supported by a neuroimaging study using fMRI to assess the real-time effects of AP on specific points. In this study, KI-3 stimulated the dorsolateral, precortical, parietal, and temporal lobes, which connect with the ventrolateral precortical lobe, which, in turn, connects to the occipital lobe and thalamus [31]. Damage in these areas can produce cognitive and visual changes, findings also observed in distemper cases [2,3,5]. Data from other neuroimaging studies have shown that different brain regions, including the hippocampus, limbic system, and cerebellum, are activated by stimulation of ST-36 and KI-3, potentially improving cognition in different neurological conditions [28,32]. EA application may also have improved cognitive function in the current study because EA has been shown to provide neuroprotection in animal models of Alzheimer's disease [33-35]. EA application at GV-20, KI-3, and ST-36 improved memory and learning in a rat model of Alzheimer's disease [36]. EA also inhibited microglial activation and decreased inflammation in rats with experimentally induced Parkinson's disease through neuroprotection of the striatum and gray matter, decreased cyclooxygenase-2, nitric oxide synthesis, and macrophage microglial activation [22]. Therefore, the combination of EA with AP in animals with CDV-induced neuronal degeneration appears logical and may be more efficacious than AP alone.

In the current study, AP treatment was started an average of 2.5 months after the onset of neurological signs. This precaution was taken to guarantee that CDV sequelae and the neurological state were stable. For this reason, the dogs received their first AP session based on hematological findings because clinical neurological signs without CBC abnormalities characterize the chronic phase. Point selection was based on the effects of AP points in the central nervous system [21] and previous canine studies that reported significant neurological benefits using similar combinations of acupoints [12,16,17].

Overall, these findings suggest that AP/EA improved

neurological function in dogs infected with CDV. Although further studies are necessary to confirm the neurological benefits of this therapy, our findings are encouraging from a clinical perspective and may help to avoid unnecessary euthanasia of animals with severe CDV-induced neurological signs. Data from epidemiological studies have demonstrated that CDV has the highest mortality and euthanasia rate among canine infectious diseases [37-39]. A previous study showed that 50% of CDV-infected dogs were unresponsive to conventional treatment, of which 37.5% were euthanized, and 14.3% died [39]. However, there are no other published studies on AP treatment for CDV sequelae, making it difficult to compare results. While untreated animals may rarely exhibit partial reversal of neurological signs [1], myoclonus is considered incurable, which conflicts with the improvement in myoclonus in this study.

This study has some limitations. It was not a controlled blinded study, which may have overestimated the AP treatment efficacy. However, considering the severity of the disease and ethical concerns, it would not be appropriate to include a negative control group. To our knowledge, there is no information in the literature regarding successful conventional treatment for CDV sequelae [4-6], making it difficult to include a positive control group. However, the inclusion of a control group is pivotal to better clarify our results since some CDV-infected dogs may exhibit partial neurological recovery even without treatment [5]. Another limitation of this study is that a necropsy could not be performed on animals for a definitive diagnosis of CDV because all patients remained alive after treatment. However, urine RT-PCR is currently the gold standard for antemortem CDV diagnosis [2,3,40]. Although CDV vaccination can produce a false-positive result, this occurs only for a short time following vaccination (approximately two days) [4,41]. Postvaccination viral excretion in the urine is rare and less common than fecal, salivary, lacrimal, and nasal secretion [41]. The apparent high sensitivity of RT-PCR in detecting CDV in the urine of dogs showing neurological signs is likely because CDV can be excreted up to 90 days after infection [4]. In this study, six of the 24 animals were vaccinated at least four weeks before testing, making it unlikely that the RT-PCR results were false positives. Other diagnostic modalities for CDV include cerebrospinal fluid collection, MRI, and CT. RT-PCR is more sensitive in urine than in CSF because the antigen is detected in CSF only during acute CDV encephalitis [4,41]. Although MRI and CT are available at our hospital, no pathognomonic imaging findings can definitively diagnose CDV infection. Therefore, at best, these would help to rule out other neurological conditions. However, CT, MRI, and cerebrospinal fluid collection require general anesthesia, which poses significant risks to the already neurologically impaired patient population of this study. In addition, other concomitant diseases, such as IVDD and ischemic myelopathy, should be considered complicating factors. IVDD does not produce central nervous system changes, and more than 70% of cases of IVDD are due to upper motor neuron lesions [2,42] characterized by limb spasticity, which was undetected in the dogs in this study. Lower motor neuron lesions are only observed in approximately 15% of IVDD cases [42]. While these could produce some of the neurological signs observed in the current study, including changes in the patellar reflex, muscular weakness, paresis or paraplegia, and superficial and deep pain sensation, our experience indicates that AP is minimally effective in these cases. In the current study, 25% of animals showed only decreased locomotor function, which could be produced by concomitant IVDD. Even if IVDD was a cause of the neurologic lesions in all these animals, improvements were also noted in the other 75% of animals whose lesions could not be accounted for by IVDD. Another possible concomitant disease with similar lower motor neuron signs is ischemic myelopathy. However, in these cases, abrupt neurological changes occur without progression [43], which was unnoticed in the current study. Finally, as this study examined patients that had recovered after acute CDV infection, randomization and blinding were impossible.

CONCLUSIONS

AP combined with EA appears to be an effective therapeutic option for neurological rehabilitation and should be considered within the chronic phase of canine distemper to improve motor and sensory functions. While definitive proof requires double-blind, clinically controlled studies, our findings are promising given the poor prognosis and lack of currently available treatment.

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AUTHORS' CONTRIBUTIONS

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P. L. Luna; Data curation, Jean Joquim, Renata Cassu, José Carlos Pantoja and Stelio P. L. Luna; Formal analysis, Bianca Santos and Stelio P. L. Luna; Funding acquisition, Bianca Santos and Stelio P. L. Luna; Investigation, Bianca Santos and Jean Joquim; Methodology, Bianca Santos, Jean Joquim, José Carlos Pantoja and Stelio P. L. Luna; Project administration, Bianca Santos and Stelio P. L. Luna; Resources, Stelio P. L. Luna; Supervision, Jean Joquim and Stelio P. L. Luna; Validation, Bianca Santos, Jean Joquim and Stelio P. L. Luna; Visualization, Bianca Santos, Jean Joquim and Stelio P. L. Luna; Writing – original draft, Bianca Santos, Jean Joquim and Stelio P. L. Luna; Writing, review and editing, Bianca Santos, Renata Cassu and Stelio P. L. Luna.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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