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Experience with 5% ethanolamine oleate for sclerotherapy of oral vascular anomalies: A cohort of 15 consecutive patients☆

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ABSTRACT

Purpose: To describe the effectiveness and safety of a sclerotherapy protocol with 5% ethanolamine oleate (EO) at 0.1 mL/3 mm for oral vascular anomalies (OVAs). Our hypothesis is that EO applied at a concentration of 5% may decrease the number of sessions necessary for clinical healing.
Materials and methods: We describe a cohort of 15 consecutive patients. OVAs <20 mm were included. Clinical data of the OVAs were collected. Descriptive and bivariate statistical analyses were performed.
Results: Fifteen of the 19 OVAs were varicosities and the lower lip was the most affected site (n = 7). The median size was 6 mm, and one session was required in 89.5% of cases for clinical healing within 28 days. The pain/burning score was low (<2) for most lesions (63.1%) and the degree of satisfaction was high (>8) for all OVAs. The number of applications, final volume of drug and time to resolution differed significantly according to the size of the anomaly.
Conclusion: The protocol with 5% EO was shown to be effective and safe to treat OVAs <20 mm, and with a decrease in the number of sessions, volume and time to resolution, without complications and with high patient satisfaction.

1. Introduction

Anomalies of vascular origin are common in the head and neck region, including the oral mucosa. Although their classification is controversial, the clinical and histological features and biological behavior form the basis for the denomination and diagnosis of these conditions (Greene, 2012). Vascular anomalies are currently divided into two groups: tumors and vascular malformations (Sham and Sultana, 2012; Colleti et al., 2014; Fowell et al., 2017).

Hemangiomas are rapidly growing benign vascular tumors of infancy that are uncommon in adolescence or adulthood. These tumors often begin proliferating shortly after birth and tend to involute spontaneously (Eivazi and Werner, 2013). Hemangiomas affect up to 10% of the pediatric population and are more prevalent in females and premature and low-birthweight infants (Haggstrom and Drolet, 2007; Drolet et al., 1999). Vascular malformations (VMs) are present at birth and affect both females and males. Their incidence in the head neck region ranges from 14% to 65% (Haggstrom and Drolet, 2007; Kobayashi et al., 2013). Unlike hemangiomas, VMs never involute. The International Society of Vascular Anomalies classifies VMs into two groups: slow-flow (venous component) and high-flow (arteriovenous component) (Fowell et al., 2017; Mulliken and Glowacki, 1982; Buckmiller et al., 2010; ISSVA, 2014). In addition, varicosities are acquired asymptomatic vascular anomalies characterized by an extensive and abnormal vein (Lazos et al., 2015). This anomaly is more common in older adults (>60 years of age) and may appear in the sublingual region, lips, and buccal mucosa (Lazos et al., 2015; Johann et al., 2005; Correa et al., 2007).

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Vascular anomalies can cause cosmetic distress, pain, ulceration, bleeding, secondary infection, tissue deformation, dental asymmetry, impaired speech, and obstruction of the upper airways (Greene, 2012; Sigaux et al., 2015). The treatment options for oral vascular anomalies (OVAs) include sclerotherapy, surgery, embolization, laser therapy, systemic corticosteroids, cryotherapy, interferon-alpha, and radiation therapy (Johann et al., 2005; Neuschl et al., 2014; Hiraoka et al., 2012; Sadick et al., 2017). The choice of treatment depends on the size, location and hemodynamics of the anomaly, degree of invasion into anatomic structures, age of the patient, and feasibility of the technique to be employed (Hiraoka et al., 2012; Hanemann et al., 2004).

Sclerotherapy is of interest for the treatment of OVAs because it is an effective and minimally invasive technique, providing healing rates of 70%–100% (Bonan et al., 2007; Pradhan and Rahman, 2011; Costa et al., 2011; da Silva et al., 2014; Fernandes et al., 2018). Although many sclerosing agents are available, such as sodium morrhuate, sodium psylliate, quinine urethrone, ethanolamine oleate (EO), polidocanol, sodium tetradecyl sulfate, hypertonic saline and absolute alcohol, EO is particularly useful because of its low toxicity compared to other sclerosis-inducing agents (Johann et al., 2005; Costa et al., 2011; Dilsiz et al., 2009). Previous studies have shown the effectiveness of different concentrations of EO (1.25%, 2.5%, and 5%) for OVA treatment (Johann et al., 2005; Costa et al., 2011; da Silva et al., 2014; Fernandes et al., 2018). However, the number of sessions and volume of EO used vary, and little is known about the complications of treatment and patient satisfaction.

Considering the effectiveness and safety data on sclerotherapy with EO reported in the literature, the objective this study was to describe the effectiveness and safety of sclerotherapy with 5% EO at 0.1 mL/3 mm for the treatment of OVAs. Complications and patient satisfaction are also reported. Our hypothesis is that EO applied at a concentration of 5% may decrease the number of sessions necessary for the complete clinical healing of OVAs.

2. Materials and methods

2.1. Ethics considerations and study approval

The study was conducted in accordance with the guidelines of the 1964 Declaration of Helsinki, and the Bioethics Committee of the Federal University of Minas Gerais approved the protocol for this study (2014/551062).

2.2. Study sample

Fifteen patients with OVAs were included in this cohort. All patients were recruited and treated consecutively at the Oral Pathology referral service of the School of Dentistry, Federal University of Minas Gerais, from 2014 to 2016.

The diagnosis of OVAs was made in accordance with the latest ISSVA (2014) classification for vascular anomalies approved by the International Society for the Study of Vascular Anomalies workshop based on clinical history, diascopy and fine-needle aspiration. The indications for treatment included pain, growth, swelling, pressure, and esthetic complaints. All anomalies diagnosed as OVAs were treated with 5% EO (Zest Farmacêutica Ltda, Rio de Janeiro, RJ, Brazil).

2.3. Protocol drug

All OVAs were treated by intralesional injection of 0.1 mL of 5% EO per 3 mm of the anomaly. This protocol was adapted according to studies in the literature, which reported the safe use of 1.25% or 2.5% EO at a dose of 1 mL for anomalies measuring 3 to 50 mm (Johann et al., 2005) and of undiluted 5% EO as a single application of 0.1 mL for the treatment of OVAs measuring 10 mm (Costa et al., 2011). The proposal of the current study was to use 5% EO without dilution to reduce the number of sessions and the final volume of drug, in addition to increasing the distribution of the sclerosing agent within the anomaly.

The vascular anomalies were first evaluated and measured to determine the volume of intralesional injection. Topical anesthetic (5% Xylocaine®:5% Lidocaine, AstraZeneca, Cotia, SP, Brazil) was applied for about 60 s, rubbing a cotton swab on the surface of the anomaly to minimize puncture discomfort and to preserve the lumen of the lesion. The drug was injected with a BD Ultra-Fine II Short Needle Insulin Syringe, 1 CC (Becton Dickinson & Company, Franklin Lakes, NJ, USA). The OVA was aspirated, reflux of venous blood was confirmed, and 0.1 mL of 5% EO was applied per 3 mm of the lesion. The patient returned within 7 days for evaluation. The interval between each application was 14 days until complete clinical healing of the OVA. A single operator performed the treatment.

2.4. Protocol outcome assessment

Demographic data of the patients (gender, age, and ethnicity) were obtained. The relevant clinical data collected included diagnosis, site and size of the anomaly, number of sessions, number of applications, final volume of drug applied, clinical healing, pain/burning, and presence or absence of edema (Amaral et al., 2012), ulcer, postoperative functional alterations (eating and/or speech), bleeding, hematoma, infection and scarring. In addition, analgesic use, time to resolution, degree of patient satisfaction with the treatment, and recurrence were investigated.

The diagnosis included varicose veins or varix (acquired OVAs), hemangiomas, and VMs. All OVAs were clinically superficial and slow-flow lesions. The size of the anomalies was measured with a millimeter ruler in unique plane and corresponded to the largest diameter of the anomaly. The number of sessions was defined as the number of times the patient was subjected to sclerotherapy. Thus, after 14 days the patients could undergo a new application. The number of applications refers to the number of points chosen for the application of 5% EO in the OVA in the same session. On the other hand, the term final volume of drug (mL) corresponds to the sum of the 5% EO used in all sessions to treat each lesion.

Clinical healing was evaluated using the scores proposed by Achauer et al. (1997). If complete clinical remission of the anomaly consisting of replacement with normal tissue did not occur after four sessions, sclerotherapy was discontinued and another treatment was proposed. Pain/burning was measured on the first day using a visual analogue scale (VAS) ranging from 0 to 10, where the left endpoint of the scale corresponds to “no pain” and the right endpoint to the “worst imaginable pain” (Mannion et al., 2007).

The patients received information about adverse effects (bleeding and edema) and were asked to avoid physical effort. In the case of atypical bleeding, the recommendation was to compress the area with gauze and to contact the research team, if necessary. The patients were instructed to use the same analgesic drug containing paracetamol (750 mg, four times per day) for pain/burning relief, if needed. All evaluations were performed 7 days after application.

In cases that required more than one session of treatment, the new application was done at an interval of 14 days and the time to resolution was determined. A VAS was used to evaluate the degree of patient satisfaction with the treatment (0 = totally unsatisfied and 10 = totally satisfied) (Peñarrocha et al., 2007). Recurrence was defined as the return of OVAs at some site 6 to 12 months after the end of treatment.

The effectiveness of treatment was evaluated based on clinical healing and recurrence. The safety of treatment was assessed in relation to pain/burning, edema, analgesic use, ulcer, postoperative functional alterations, bleeding, hematoma, infection, scarring, and degree of patient satisfaction with the treatment.

2.5. Statistical analysis

Descriptive and bivariate statistical analyses were performed using the SPSS 17.0 for Windows software (SPSS, Inc., Chicago, IL, USA). Quantitative variables were categorized according to median to investigate associations. The dependent variable was the median size of the OVAs and the independent variables were the number of sessions, number of applications, final volume of drug, pain/burning, time to resolution, and degree of patient satisfaction with the treatment. Fisher's exact test was applied to determine significant differences between the categorical variables considering $p < 0.05$.

3. Results

A total of 15 patients and 19 lesions were enrolled in the study, because 4 patients had 2 lesions each. The patients included 8 women and 7 men ranging in age from 45 to 86 years (64.3 ± 11.6). Most patients were of African descent (66.7%). Fifteen (78.9%) of the 19 OVAs were diagnosed as varicosities (78.9%), which ranged in size from 3 to 20 mm (median = 6 mm). The sites most commonly affected were the lower lip (n = 7, 36.8%) and cheek (n = 5, 26.3%). The demographic data, clinical features and main outcomes of treatment with 5% EO are shown in Table 1.

A single session was sufficient for clinical remission of most OVAs (n = 17, 89.5%). The number of applications ranged from 1 to 7 points (median = 2), with a predominance of OVAs treated at only 1 point (n = 9; 47.4%). The final volume of drug ranged from 0.1 to 0.7 mL (median = 0.2 mL). Fig. 1 shows the clinical aspect of the OVA pre- and post-sclerotherapy with 5% EO.

All 19 OVAs exhibited complete clinical healing, with the observation of an excellent response (75–100% cure) within 28 days (median = 14 days). Pain/burning up to 48 h was reported by 57.9% (n = 11) of the patients. The pain VAS score ranged from 0 to 7, with a median of 2. Mild edema persisted for 48 h in 100% of the OVAs, and hardening at the treated site was reported. Ulcers, postoperative functional alterations, bleeding, hematoma, infection or scarring was not observed in any case. None of the patients required analgesic drugs. The scores of patient satisfaction were 9 and 10 in 94.7% of the anomalies. Recurrence was not observed during the 12 months of clinical follow-up.

Bivariate analysis was used to compare the groups according to median size (6 mm) of the OVAs and independent variables (Table 2). Pain/burning and satisfaction scores were similar in the two groups. The number of sessions also did not differ, but the number of applications was significantly smaller in anomalies measuring 6 mm or less. Consequently, the final volume applied and the times to resolution were significantly lower in the group with small OVAs.

4. Discussion

This cohort describes a sclerotherapy protocol for the treatment of OVAs using 0.1 mL of 5% EO per approximately 3 mm of the lesion. Our results suggest the 5% EO used in pure form may decrease the number of sessions until complete clinical healing of the OVA, because only 10.5% of the 19 OVAs required a second session for clinical remission. Costa et al. (2011), studying 66 OVAs, also observed a decrease in the number of sessions when they applied 5% EO at a proportion of 0.1 mL/10 mm of lesion. However, despite the success with only one session in more than half of the lesions, a new session was necessary in 46% of the anomalies. A recent study using a similar protocol of undiluted 5% EO (0.3 mL per 10 mm of the lesion) also observed a decrease in the number of sessions. However, 40% of the cases required another application (Fernandes et al., 2018). The difference compared to our results may be due to the greater size of the lesions or infiltration of the anesthetic with a vasoconstrictor around the lesion. Although decreasing pain, this infiltration can hamper the view of clinical limits of the anomaly and vasoconstriction can alter the action of the drug. *In vivo* studies should be encouraged to clarify these issues about anesthetic infiltration.

Since the safety of application of 5% EO respecting the dose limits has been demonstrated, we standardized the dose according to the smaller size of the anomaly using a ratio of 0.1 mL/3 mm of the lesion in order to better distribute the drug throughout the

Table 1
Characteristics of the patients and oral vascular anomalies treated with 5% ethanolamine oleate.

Patient (n = 15)	Age (years) (64.3 ± 11.6)	Gender	Ethnicity	Diagnosis (n = 19)	Site	Size (mm)	No. of sessions	No. of applications	Final volume of drug (mL)
1	71	M	African descent	Varicose	Alveolar mucosa	7	2	2	0.4
2	54	F	African descent	Varicose	Lower lip	5	1	1	0.1
3	45	F	African descent	Varicose	Lower lip	3	1	1	0.1
4	73	F	African descent	Varicose	Cheek	13	1	4	0.4
5	47	M	Caucasian	Venous VM	Palate	12	1	4	0.4
6	73	M	African descent	Varicose	Cheek	5	1	1	0.1
7	67	M	African descent	Venous VM	Cheek	14	1	4	0.4
8	86	M	Caucasian	Varicose	Upper lip	5	1	1	0.1
				Varicose	Tongue	10	1	3	0.3
9	68	M	African descent	Varicose	Cheek	8	1	2	0.2
10	59	F	African descent	Venous VM	Palate	20	1	7	0.7
11	61	M	African descent	Varicose	Lower lip	4	1	1	0.1
				Varicose	Lower lip	6	1	2	0.2
12	58	F	Caucasian	Varicose	Lower lip	3	2	1	0.2
				Varicose	Lower lip	3	1	1	0.1
13	54	F	African descent	Venous VM	Cheek	12	1	4	0.4
14	79	F	Caucasian	Varicose	Tongue	5	1	1	0.1
				Varicose	Lower lip	5	1	1	0.1
15	70	F	Caucasian	Varicose	Tongue	10	1	3	0.3

M, male; F, female; VM, vascular malformation.

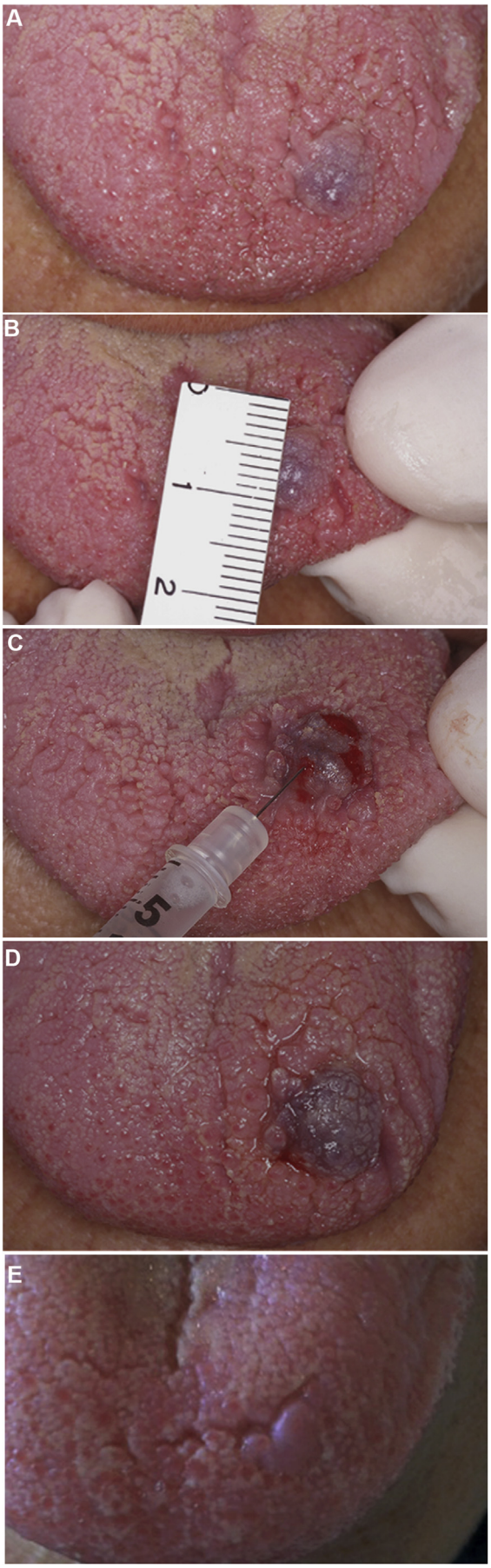

Table 2
Comparison between variables of the treatment protocol using 5% ethanolamine oleate and size of the oral vascular anomaly.

Variable		Size of oral vascular anomaly		*p*-value[a]
		≤6 mm (n = 10)	>6 mm (n = 9)	
Number of sessions	1	9	8	0.737
	2	1	1	
Number of applications (median = 2)	≤2	10	2	**0.001**
	>2	0	7	
Final volume of drug (mL) (median = 0.2)	≤0.2	10	1	**<0.001**
	>0.2	0	8	
Pain/burning scale (median = 2)	≤2	6	6	0.570
	>2	4	3	
Satisfaction score (median = 10)	9 or 8	4	2	0.370
	10	6	7	
Time to resolution (days) (median = 14)	≤14	9	3	**0.017**
	>14	1	6	

Bold indicates *p*-values are statistically significant.
[a] Fisher's exact test, $p < 0.05$: statistically significant difference.

anomaly. A single puncture may not be sufficient to distribute the sclerosing agent evenly throughout the lesion. As expected, our results showed a significant difference in the number of applications and final volume of drug administered in a single session between lesions larger and smaller than 6 mm. These results corroborate the findings of Fernandes et al. (2018) who compared OVAs of different sizes. In the present study, although the volume of EO was increased by 0.3 every 10 mm, compared to the study of Costa et al. (2011) the safe limit of the EO dose, which is 20 mL in adult patients or 0.3 mL/kg (Ozaki et al., 2010), was maintained.

Ethanolamine oleate is a low-cost sclerosing agent (Qiu et al., 2013) that is used to treat vascular anomalies in the oral cavity and other sites of the body, but no standard concentration has been established (Das and Hoque, 2008; Nishida et al., 1999). Good treatment responses have been observed for OVAs treated with (Bonan et al., 2007; Pradhan and Rahman, 2011; da Silva et al., 2014) or undiluted EO (Costa et al., 2011; Fernandes et al., 2018). However, the number of sessions is variable, ranging from 1 to 10 (Johann et al., 2005; da Silva et al., 2014). Concentrations of EO of 1.25% and 2.5% can result in a larger volume of fluid inside the lesion, along with repeated adverse effects due to the need for a second or more sessions. These facts are often poorly tolerated by the patient, who may even abandon treatment. Reducing the frequency of exposure of the patients to the adverse effects of sclerotherapy was one of the objectives of this protocol, despite the inconvenient need for more punctures in anomalies larger than 6 mm.

Ethanolamine oleate is an unsaturated fatty acid that acts as a sclerosant when injected intravenously (Choi et al., 2002). The drug primarily causes irritation to the intima of the endothelium and produces a sterile inflammatory response, resulting in fibrosis of the vessel wall or possible vein occlusion (Nishida et al., 1999). Ethanolamine oleate also diffuses rapidly through the vessel wall and produces extravascular inflammation (da Silva et al., 2014; Kaji et al., 2009). The clinical signs and symptoms reported after sclerotherapy include pain or burning sensation, edema, and subsequent hardening at the site of the anomaly (Costa et al., 2011). These findings were also observed in our study as part of the chemical action of EO. The most common pain score was 2, but there was no difference according to the size of the anomaly.

Fig. 1. Oral vascular anomaly (varicose) in the tongue. (A) Initial clinical appearance; (B) measurement with a millimeter ruler; (C) intralesional injection of 0.1 mL of 5% ethanolamine oleate per 3 mm of anomaly; (D) vascular anomaly immediately after sclerotherapy; (E) clinical appearance after 28 days.

However, treatment with 5% EO has also been shown to produce a low pain score in larger lesions. Edema was observed in the treated OVAs for up to 48 h, in agreement with other studies (Hiraoka et al., 2012; Costa et al., 2011) that used 5% EO at 0.1 mL/cm and 2.5% EO at 0.2 mL/cm. However, the persistence of edema up to 72 h was reported when a concentration of 1.25% or 2.5% EO at a dose of 1 mL was used (Johann et al., 2005; Pradhan and Rahman, 2011). The longer duration of swelling was probably due to the volume applied (1 mL) rather than the concentration of the drug. The advantage of this protocol is the lower volume of EO, which may decrease the duration of edema.

Some local complications such as ulceration, bleeding and necrosis can occur after the application of EO to treat vascular anomalies. In a series of 8 cases of OVAs treated by sclerotherapy using 1.25% EO, there was only one patient with superficial ulceration (da Silva et al., 2014). In another study, three of 53 cases developed ulceration after the application of 5% EO which, according the authors, healed spontaneously within 5 days (Costa et al., 2011). Systemic complications such as anaphylactic reactions, hemoglobinuria, nerve damage or cardiovascular collapse can be observed in this type of treatment (Johann et al., 2005; Costa et al., 2011; Kaji et al., 2009; Bordas et al., 1989). This study found no local or systemic complications, probably because the OVAs were small and superficial, blood flow was low, and a smaller volume of the drug was used. No complications were observed with the use of undiluted 5% EO in OVAs measuring 10–35 mm (Fernandes et al., 2018). The size of the lesion, concentration dosage, intravascular application of the sclerosant and the number of applications must be considered to prevent necrosis/ulcer. Moreover, professional experience with performing adequate technique is important to avoid adverse effects of the drug.

Another significant difference between the size groups of the abnormalities was the time to clinical resolution. Complete remission was observed within 14 days in lesions smaller than 6 mm but required up to 30 days in the larger lesions. The time to resolution seems to be longer when a concentration of 1.25% or 2.5% is used. If we consider, for example, four applications at intervals of 14 days, healing can take 2 months. It is important to reduce this period to ensure patient adherence to treatment. A rapid clinical outcome or clinical remission can increase patient satisfaction, as observed in the present study for the two groups.

5. Conclusion

This cohort had some limitations such as the reduced sample number and restricted size of the anomalies, which prevent generalized conclusions. The treatment proposed using 5% EO (0.1 mL/3 mm of the lesion) to treat OVAs smaller than 20 mm showed effective and safe and suggests a decrease in the number of sessions, final volume of drug and time to resolution, without complications and with high patient satisfaction. Although the number of studies using 5% EO is still small, clinical trials should be encouraged to gather evidence of the actual efficacy of this concentration.

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Author contributions

This study was performed in collaboration among all authors. Mesquita designed the study. Amaral and Ribeiro collected the data. Grossmann, Aguiar and Amaral analyzed and interpreted the data. Kato and Ribeiro wrote the first draft of the article. Mesquita and Aguiar drafted and revised the article. The research consortium completed the final manuscript. Each author read and approved the final manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

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